STIC Search Report
Biotech-Chem Library

STIC Database Tracking Number: 130820

TO: Zohreh Fay **Location: 3a61 / 3c70** **Wednesday, September 01, 2004** **Art Unit: 1614** **Phone: 272-0573** **Serial Number: 10 / 694309**	**From: Jan Delaval** **Location: Biotech-Chem Library** **Rem 1A51** **Phone: 272-2504** **jan.delaval@uspto.gov**

Search Notes

Access DB# 130820

SEARCH REQUEST FORM

Scientific and Technical Information Center

Requester's Full Name: Zohreh Fay Examiner #: 66646 Date: 8/25/04
Art Unit: 1614 Phone Number (571) 272-0572 Serial Number: 10/694,309
Mail Box and Bldg Room Location: 3C70/3461 Results Format Preferred (circle): PAPER DISK E-MAIL

If more than one search is submitted, please prioritize searches in order of need.

Please provide a detailed statement of the search topic, and describe as specifically as possible the subject matter to be searched. Include the elected species or structures, keywords, synonyms, acronyms, and registry numbers, and combine with the concept or utility of the invention. Define any terms that may have a special meaning. Give examples or relevant citations, authors, etc. if known. Please attach a copy of the cover sheet, pertinent claims, and abstract.

Title of Invention: Histone ~~Deacetylase~~ Deacetylase inhibitors for treating degenerative Diseases of the eye

Inventors (please provide full names): Helberg, Peggy E.

Earliest Priority Filing Date: 11/12/02

**For Sequence Searches Only* Please include all pertinent information (parent, child, divisional, or issued patent numbers) along with the appropriate serial number.*

please search the claimed method of use.

JA

STAFF USE ONLY	Type of Search	Vendors and cost where applicable
Searcher JA	NA Sequence (#)	STN ✓
Searcher Phone #: 22504	AA Sequence (#)	Dialog
Searcher Location:	Structure (#)	Questel/Orbit
Date Searcher Picked Up: 9/1	Bibliographic ✓	Dr.Link
Date Completed: 9/1	Litigation	Lexis/Nexis
Searcher Prep & Review Time:	Fulltext	Sequence Systems
Clerical Prep Time: 40	Patent Family	WWW/Internet
Online Time: 145	Other	Other (specify)

PTO-1590-8 (10-2003)

=>
=> fil biosis
FILE 'BIOSIS' ENTERED AT 09:27:44 ON 01 SEP 2004

FILE COVERS 1969 TO DATE.
CAS REGISTRY NUMBERS AND CHEMICAL NAMES (CNs) PRESENT
FROM JANUARY 1969 TO DATE.

RECORDS LAST ADDED: 26 August 2004 (20040826/ED)

FILE RELOADED: 19 October 2003.

=> d all tot l31

L31 ANSWER 1 OF 3 BIOSIS COPYRIGHT (c) 2004 The Thomson Corporation. on STN
AN **2002:479722** BIOSIS
DN **PREV200200479722**
TI The family of retinoblastoma proteins.
AU Stiegler, Peter; Giordano, Antonio [Reprint author]
CS Department of Pathology, Anatomy and Cell Biology, Thomas Jefferson University, 1020 Locust Street, Room 226, Philadelphia, PA, 19107, USA
agiordan@lac.jci.tju.edu
SO Critical Reviews in Eukaryotic Gene Expression, (2001) Vol. 11, No. 1-3, pp. 59-76. print.
CODEN: CRGEEJ. ISSN: 1045-4403.
DT Article
General Review; (Literature Review)
LA English
ED Entered STN: 11 Sep 2002
Last Updated on STN: 11 Sep 2002
CC Biochemistry studies - General 10060
Sense organs - Pathology 20006
Neoplasms - Pathology, clinical aspects and systemic effects 24004
IT Major Concepts
Biochemistry and Molecular Biophysics; Tumor Biology
IT Diseases
retinoblastoma: eye disease, neoplastic disease
Retinal Neoplasms (MeSH); Retinoblastoma (MeSH)
IT Chemicals & Biochemicals
E2F; **histone deacetylases**; pRB/p105; pRB2/p130; pRBL1/p107; pocket proteins; retinoblastoma proteins
IT Miscellaneous Descriptors
deacetylation; transcription
ORGN Classifier
Mammalia 85700
Super Taxa
Vertebrata; Chordata; Animalia
Organism Name
mammal
Taxa Notes
Animals, Chordates, Mammals, Nonhuman Vertebrates, Nonhuman Mammals, Vertebrates
RN **9076-57-7 (histone deacetylases)**

L31 ANSWER 2 OF 3 BIOSIS COPYRIGHT (c) 2004 The Thomson Corporation. on STN
AN **2002:91231** BIOSIS
DN **PREV200200091231**
TI **Histone deacetylase** inhibitors block cell cycle progression by induction of retinoblastoma protein hypophosphorylation in coronary smooth muscle cells.
AU Skaletz-Rorowski, A. [Reprint author]; Peters, K.; Eschert, H.; Koelle, D. E.; Loidl, P.; Breithardt, G.; Jung, M.

CS Inst. for Arteriosclerosis Research, Muenster, Germany
SO European Heart Journal, (September, 2001) Vol. 22, No. Abstract Supplement, pp. 284. print.
Meeting Info.: XXIII Congress of the European Society of Cardiology together with the 36th Annual General Meeting of the Association for European Paediatric Cardiology. Stockholm, Sweden. September 01-05, 2001.
CODEN: EHJODF. ISSN: 0195-668X.
DT Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
Conference; (Meeting Poster)
LA English
ED Entered STN: 24 Jan 2002
Last Updated on STN: 25 Feb 2002
CC General biology - Symposia, transactions and proceedings 00520
Cytology - Human 02508
Biochemistry studies - Nucleic acids, purines and pyrimidines 10062
Biochemistry studies - Proteins, peptides and amino acids 10064
Enzymes - General and comparative studies: coenzymes 10802
Pathology - Therapy 12512
Cardiovascular system - Physiology and biochemistry 14504
Sense organs - Pathology 20006
Pharmacology - General 22002
Pharmacology - Clinical pharmacology 22005
Neoplasms - Pathology, clinical aspects and systemic effects 24004
IT Major Concepts
Cardiovascular System (Transport and Circulation); Pharmacology
IT Diseases
retinoblastoma: eye disease, neoplastic disease
Retinal Neoplasms (MeSH); Retinoblastoma (MeSH)
IT Chemicals & Biochemicals
DNA; MD85: enzyme inhibitor-drug; cyclin/cyclin-dependent kinase; fetal calf serum; histone: hyperacetylation; **histone deacetylase**: inhibition; mitogen-activated protein kinase: activation; p21: expression; retinoblastoma gene product: phosphorylation; retinoblastoma protein: phosphorylation; trichostatin A: enzyme inhibitor-drug; tritiated thymidine
IT Miscellaneous Descriptors
cell cycle progression; Meeting Abstract; Meeting Poster
ORGN Classifier
Hominidae 86215
Super Taxa
Primates; Mammalia; Vertebrata; Chordata; Animalia
Organism Name
hcSMC cell line: human coronary smooth muscle cells
Taxa Notes
Animals, Chordates, Humans, Mammals, Primates, Vertebrates
RN **9076-57-7 (histone deacetylase)**
142243-02-5 (mitogen-activated protein kinase)
58880-19-6 (trichostatin A)
50-88-4 (tritiated thymidine)

L31 ANSWER 3 OF 3 BIOSIS COPYRIGHT (c) 2004 The Thomson Corporation. on STN
AN **1998:498084** BIOSIS
DN **PREV199800498084**
TI **Histone deacetylase** and the retinoblastoma protein.
AU Magnaghi-Jaulin, L. [Reprint author]; Groisman, R.; Naguibneva, I.; Robin, P.; Trouche, D.; Harel-Bellan, A.
CS Lab. Oncogenese, Differenciation Transduction du signal, CNRS UPR 9079, IFC-01, 94801 Villejuif, France
SO Bulletin du Cancer (Paris), (July, 1998) Vol. 85, No. 7, pp. 606-607. print.
CODEN: BUCABS. ISSN: 0007-4551.
DT Article

LA French
ED Entered STN: 18 Nov 1998
Last Updated on STN: 18 Nov 1998
AB The balance between cellular proliferation and differentiation is strictly controlled in the cell and the deregulation of this balance can lead to tumour formation. The tumour suppressor protein Rb plays a key role in this balance essentially by repressing progression through the cell cycle and there by it blocks the cell in G1 phase. Rb represses S phase genes through the recruitment of an enzyme which modifies DNA structure, the **histone deacetylase** HDAC1. The Rb/HDAC1 complex is a key element in the control of cell proliferation and differentiation. Moreover, this complex is likely to be a target for transforming viral proteins.
CC Neoplasms - Carcinogens and carcinogenesis 24007
Genetics - Animal 03506
Enzymes - Physiological studies 10808
Metabolism - Proteins, peptides and amino acids 13012
Sense organs - Pathology 20006
Neoplasms - Biochemistry 24006
Cytology - Animal 02506
Biochemistry studies - Proteins, peptides and amino acids 10064
IT Major Concepts
Molecular Genetics (Biochemistry and Molecular Biophysics); Tumor Biology
IT Chemicals & Biochemicals
histone deacetylase: carcinogenesis mechanism, retinoblastoma tumor suppressor protein complex formation
ORGN Classifier
Animalia 33000
Super Taxa
Animalia
Organism Name
animal: animal model
Taxa Notes
Animals
RN **9076-57-7 (histone deacetylase)**

=> => fil reg
FILE 'REGISTRY' ENTERED AT 09:56:25 ON 01 SEP 2004
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.

Property values tagged with IC are from the ZIC/VINITI data file provided by InfoChem.

STRUCTURE FILE UPDATES: 30 AUG 2004 HIGHEST RN 736108-36-4
DICTIONARY FILE UPDATES: 30 AUG 2004 HIGHEST RN 736108-36-4

TSCA INFORMATION NOW CURRENT THROUGH MAY 21, 2004

Please note that search-term pricing does apply when conducting SmartSELECT searches.

Crossover limits have been increased. See HELP CROSSOVER for details.

Experimental and calculated property data are now available. For more information enter HELP PROP at an arrow prompt in the file or refer to the file summary sheet on the web at:
http://www.cas.org/ONLINE/DBSS/registryss.html

=> d ide can l1

L1 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2004 ACS on STN
RN 9076-57-7 REGISTRY
CN Deacetylase, histone (9CI) (CA INDEX NAME)
OTHER NAMES:
CN **Histone deacetylase**
MF Unspecified
CI MAN
LC STN Files: ADISNEWS, AGRICOLA, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CAPLUS, CASREACT, CEN, CIN, EMBASE, PROMT, TOXCENTER, USPAT2, USPATFULL
DT.CA CAplus document type: Book; Conference; Dissertation; Journal; Patent; Report
RL.P Roles from patents: ANST (Analytical study); BIOL (Biological study); MSC (Miscellaneous); OCCU (Occurrence); PREP (Preparation); PROC (Process); PRP (Properties); USES (Uses)
RLD.P Roles for non-specific derivatives from patents: BIOL (Biological study); OCCU (Occurrence); PROC (Process); USES (Uses)
RL.NP Roles from non-patents: ANST (Analytical study); BIOL (Biological study); FORM (Formation, nonpreparative); MSC (Miscellaneous); OCCU (Occurrence); PREP (Preparation); PROC (Process); PRP (Properties); RACT (Reactant or reagent); USES (Uses); NORL (No role in record)
RLD.NP Roles for non-specific derivatives from non-patents: BIOL (Biological study); OCCU (Occurrence); PREP (Preparation); PROC (Process); PRP (Properties)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
2064 REFERENCES IN FILE CA (1907 TO DATE)
34 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
2085 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1: 141:157117

REFERENCE 2: 141:156906

REFERENCE 3: 141:155789

REFERENCE 4: 141:154894

REFERENCE 5: 141:154713

REFERENCE 6: 141:152938

REFERENCE 7: 141:152022

REFERENCE 8: 141:151891

REFERENCE 9: 141:151185

REFERENCE 10: 141:150974

=> d his

(FILE 'HOME' ENTERED AT 09:11:48 ON 01 SEP 2004)
SET COST OFF

FILE 'REGISTRY' ENTERED AT 09:11:59 ON 01 SEP 2004
E HISTONE DEACETYLASE/CN
L1 1 S E3
L2 313 S HISTONE DEACETYLASE
L3 312 S L2 NOT L1

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     FILE 'HCAPLUS' ENTERED AT 09:12:30 ON 01 SEP 2004
L4          2086 S L1
L5           263 S L3
L6          3002 S HISTONE DEACETYLASE
L7             4 S HISTONE DE ACETYLASE
L8             1 S HISTONEDEACETYLASE
L9          3146 S L4-L8
                 E EYE, DISEAE/CT
                 E E4+ALL
L10            0 S L9 AND E8,E9
L11           13 S L9 AND E7+NT
                 E E121+ALL
L12           16 S L9 AND E8,E7+NT
L13           21 S L9 AND (E26+OLD,NT,PFT,RT OR E27+OLD,NT,PFT,RT OR E28+OLD,NT,
L14           21 S L11-L13
L15           15 S L14 AND GENETIC?/SC,SX
L16            6 S L14 NOT L15
L17            5 S L16 NOT DROSOPHILA/TI
L18            1 S US20040092431/PN OR (WO2003-US33873 OR US2002-425576#)/AP,PRN
                 E HELLBERG P/AU
L19           27 S E3,E4,E8,E9
                 E HELLBERG M/AU
L20            1 S L19,L18 AND L9
L21            5 S L17,L20
L22           26 S L19 NOT L21
L23            5 S L21 AND L4-L22

     FILE 'BIOSIS' ENTERED AT 09:23:37 ON 01 SEP 2004
                 E HELLBERG/AU
L24           20 S E48,E51
L25         2986 S L9
L26            0 S L24 AND L25
L27           13 S L25 AND (EYE+NT OR EYE DISEASE+NT)/CT
L28           23 S L25 AND (2000# OR 22031)/CC
L29           23 S L27,L28
L30           15 S L29 AND PY<=2002
                 SEL DN AN 4 6 13
L31            3 S L30 AND E1-E6

     FILE 'BIOSIS' ENTERED AT 09:27:44 ON 01 SEP 2004

     FILE 'MEDLINE' ENTERED AT 09:27:53 ON 01 SEP 2004
L32         2852 S L9
                 E HISTONE/CT
                 E E9+ALL
L33         2004 S E6+NT
L34         2004 S E6/CN
L35           15 S HDAC PROTEIN
L36         2852 S L32-L35
L37            9 S L36 AND (EYE+NT OR EYE DISEASES+NT)/CT
L38            6 S L37 AND PY<=2002

     FILE 'EMBASE' ENTERED AT 09:30:03 ON 01 SEP 2004
L39         2538 S L9
                 E HISTONE/CT
L40         2168 S E63-E130
                 E E92+ALL
L41          771 S E1
L42         2538 S L39-L41
                 E EYE/CT
L43            2 S L42 AND E3+NT
                 E EYE DISEASE/CT
L44           22 S L42 AND E3+NT
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                E OPHTHALMIC AGENT/CT
                E E3+ALL
L45           38 S L42 AND E2+NT
L46           60 S L43-L45
L47           28 S L46 AND PY<=2002
L48           11 S L41 AND L47
L49           17 S L47 NOT L48

     FILE 'WPIX' ENTERED AT 09:33:24 ON 01 SEP 2004
L50            1 S L18
L51          240 S L6/BIX OR L7/BIX OR L8/BIX
L52        18960 S (B14-N03 OR C14-N03 OR B12-L04 OR C12-L04)/MC
L53        17920 S P922/M0,M1,M2,M3,M4,M5,M6
L54         4513 S A61P027/IPC
L55        24403 S L52-L54
L56           29 S L51 AND L55
L57            8 S L56 AND PY<=2002
L58           28 S L56 AND PRY<=2002
L59           15 S L56 AND AY<=2002
L60           28 S L57-L59
L61           28 S L50,L60

     FILE 'REGISTRY' ENTERED AT 09:56:25 ON 01 SEP 2004

=> fil wpix
FILE 'WPIX' ENTERED AT 09:56:39 ON 01 SEP 2004
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FILE LAST UPDATED:          26 AUG 2004      <20040826/UP>
MOST RECENT DERWENT UPDATE:     200455        <200455/DW>
DERWENT WORLD PATENTS INDEX SUBSCRIBER FILE, COVERS 1963 TO DATE

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    HIT STRUCTURES WITHIN THE BIBLIOGRAPHIC DOCUMENT  <<<

=> d l61 all abeq tech abex tot

L61  ANSWER 1 OF 28  WPIX COPYRIGHT 2004 THOMSON DERWENT on STN
AN   2004-460979 [43]    WPIX
DNC  C2004-172131
TI   Delivering a gene product to an eye, useful for treating ocular-related
     disorders, e.g. glaucoma, comprises administering to an eye of an animal a
     first expression vector that transduces at least one ocular cell.
DC   B04 D16
IN   BROUGH, D E; KOVESDI, I; MCVEY, D L; WEI, L
PA   (GENV-N) GENVEC INC
CYC  106
```

PI WO 2004050027 A2 20040617 (200443)* EN 88 A61K000-00
RW: AT BE BG BW CH CY CZ DE DK EA EE ES FI FR GB GH GM GR HU IE IT KE LS LU MC MW MZ NL OA PT RO SD SE SI SK SL SZ TR TZ UG ZM ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NI NO NZ OM PG PH PL PT RO RU SC SD SE SG SK SL SY TJ TM TN TR TT TZ UA UG US UZ VC VN YU ZA ZM ZW
ADT WO 2004050027 A2 WO 2003-US38169 20031201
PRAI **US 2002-430617P 20021202**
IC ICM A61K000-00
AB WO2004050027 A UPAB: 20040709
NOVELTY - Delivering a gene product to an eye comprises administering to an eye of an animal a first expression vector comprising a nucleic acid sequence operably linked to a promoter and encoding a gene product, such that the expression vector transduces at least one ocular cell and the nucleic acid sequencers transcribed to produce a gene product.
DETAILED DESCRIPTION - The method comprises:
(a) administering to an eye of an animal a first expression vector comprising a nucleic acid sequence operably linked to a promoter and encoding a gene product, such that the expression vector transduces at least one ocular cell and the nucleic acid sequencers transcribed to produce a gene product; and
(b) subsequently upregulating transcription of the nucleic acid sequence in the ocular cell, with the proviso that upregulating transcription does not comprise administering a pyrogen.
INDEPENDENT CLAIMS are included for the following:
(1) prophylactically or therapeutically treating an animal for an ocular-related disorder; and
(2) delivering a gene product to a mammal.
ACTIVITY - Ophthalmological; Cytostatic. No biological data given.
MECHANISM OF ACTION - Gene therapy.
USE - The methods, nucleic acid and expression vectors are useful for prophylactically or therapeutically treating an animal for an ocular-related disorder, e.g. ocular neovascularization, age-related macular degeneration, retinal tumors, diabetic retinopathy, macular edema, glaucoma or a retinal degenerative disease (claimed).
Dwg.0/4
FS CPI
FA AB; DCN
MC CPI: B04-B01B; B04-E01; B04-E03; B04-E04; B04-E08; B04-F0100E; B04-F1100E; B04-H0100E; B04-M01; B04-N0200E; B05-A01B; B10-B02A; B10-E04A; B14-H01B; **B14-N03**; B14-S03; D05-H08; D05-H12A; D05-H12D5; D05-H12D6; D05-H12E; D05-H14
TECH UPTX: 20040709
TECHNOLOGY FOCUS - BIOTECHNOLOGY - Preferred Method: Delivering a gene product to an eye alternatively comprises administering to an eye of an animal a first expression vector comprising a nucleic acid sequence operably linked to a promoter and encoding a gene product, such that the expression vector transduces at least one ocular cell and the nucleic acid sequence is transcribed to produce a gene product, and subsequently upregulating transcription of the nucleic acid sequence in the ocular cell by exposing the ocular cell to saline, trehalose, a protein, a nucleic acid, a lipid, a steroid derivative, diclofenac sodium and misoprostol, dixlurenac, combretastatin, a protein kinase C (PKC) inhibitor, a tyrosine kinase inhibitor, hyaluronic acid, a second expression vector, a **histone deacetylase** inhibitor, retinoic acid, cold, light, radiation, microwaves, ultrasound, or physical trauma. Prophylactically or therapeutically treating an animal for an ocular-related disorder comprises administering to the animal a first expression vector comprising a nucleic acid sequence encoding an inhibitor of angiogenesis and/or a neurotrophic agent such that the expression vector transduces at least one ocular cell and the nucleic acid sequence

is transcribed, and subsequently upregulating transcription of the nucleic acid sequence, thus upregulating expression of the inhibitor of angiogenesis and/or a neurotrophic agent to prophylactically or therapeutically treat the animal for an ocular-related disorder. Upregulating transcription of the nucleic acid sequence comprises administering a non-pyrogen activator after administering the first expression vector. The method alternatively comprises contacting an ocular cell with an adenoviral vector comprising a nucleic acid sequence operably linked to a cellular promoter and encoding an inhibitor of angiogenesis and/or a neurotrophic agent, thus resulting in the production of the inhibitor of angiogenesis and/or the neurotrophic agent to prophylactically or therapeutically treat the animal for an ocular-related disorder, with the proviso that, if the adenoviral vector is administered to a mouse at a dose of 2 particles, the level of transcription of the nucleic acid sequence is not diminished more than three-fold at 28 days post-administration of the adenoviral vector compared to the level of transcription of the nucleic acid sequence at one day post-administration of the adenoviral vector. The adenoviral vector comprises a nucleic acid sequence encoding an inhibitor of angiogenesis and a nucleic acid sequence encoding neurotrophic agent. The nucleic acid sequence encoding the inhibitor of angiogenesis and the nucleic acid sequence encoding the neurotrophic agent are the same nucleic acid sequence. The adenoviral vector is replication-deficient. Delivering a gene product to a mammal comprises administering to a mammal an expression vector comprising a first nucleic acid sequence operably linked to a promoter, such that the expression vector transduces a host cell and the first nucleic acid sequence is transcribed to produce a gene product, and a second nucleic acid sequence operably linked to a promoter and encoding a retinoic acid receptor, such that the second nucleic acid sequence is transcribed in the host cell to produce the retinoic acid receptor, and subsequently administering to the mammal a retinoic acid, thus upregulating transcription of the first nucleic acid sequence in the host cell. The first expression vector is an adenoviral vector. The adenoviral vector is replication-deficient. The method alternatively comprises administering to the mammal an adenoviral vector deficient in all replication-essential gene functions of the E4 region of the adenoviral genome and comprising a nucleic acid sequence operably linked to a promoter and encoding a gene product, such that the adenoviral vector transduces a host cell and the nucleic acid sequence is transcribed to produce a gene product, and subsequently upregulating transcription of the nucleic acid sequence in the host cell, with the proviso that upregulating transcription does not comprise administering a pyrogen, an adenoviral vector, or radiation. The adenoviral vector is deficient in at least one replication-essential gene function of the E1 region of the adenoviral genome of the adenoviral vector. The adenoviral vector is deficient in at least one replication-essential gene function of the E4 region of the adenoviral genome of the adenoviral vector. All or part of the E1 and/or E4 region of the adenoviral genome of the adenoviral vector is removed. The transcription is upregulated two or more times. The transcription is upregulated at least once within one day, or seven, 14 or 28 days; or 3, 6, or 12 months of administering the first expression vector or adenoviral vector. The level of transcription of the nucleic acid sequence is at least 2-fold, 5-fold, 10-fold, 20-fold, 50-fold, or 100-fold greater than the level of transcription of the nucleic acid sequence absent the upregulation of transcription. The level of transcription of the nucleic acid sequence at one day post-upregulating transcription is at least 20, 50, or 100% the level of transcription of the nucleic acid sequence one day post-administration of the first expression vector or adenoviral vector. The upregulating transcription comprises inducing a stress response in the ocular cell or host cell; exposing the ocular cell or host cell to cold, light, radiation, microwaves, ultrasound, or physical trauma; administering to the animal one or more exogenous materials selected from the group consisting of a second expression vector, saline,

trehalose, a protein, a nucleic acid, and a drug; or administering to the animal a disaccharide. The exogenous material is a second expression vector, and second expression vector is an adenoviral vector not comprising the nucleic acid sequence. The adenoviral vector is deficient in all replication-essential gene functions of the E4 region of the adenoviral genome. The exogenous material is a protein, and the protein is a cytokine, an inhibitor of angiogenesis, a neurotrophic agent, an enzyme, or an antibody. The exogenous material is an inhibitor of angiogenesis, and the inhibitor of angiogenesis is soluble fit (s-flt) or pigment epithelium-derived factor (PEDF). The exogenous material is a nucleic acid, and the nucleic acid is an aptamer or siRNA. The exogenous material is a drug, and the drug is an immunosuppressant, a steroid, a steroid derivative, dixlurenac, combretastatin, a protein kinase C (PKC) inhibitor, a tyrosine kinase (TK) inhibitor, a Cox-I inhibitor, a Cox-II inhibitor, an anti-inflammatory, aspirin, a **histone deacetylase** inhibitor, a retinoic acid, or hyaluronic acid. The exogenous material is a drug, e.g. a prostaglandin analogue, a beta-blocker, hyaluronidase, pegaptanib sodium, tetrahydrozoline hydrochloride, or dorzolamide hydrochloride. Upregulating transcription comprises administering to the animal a retinoic acid, or **histone deacetylase** inhibitor and a retinoic acid. The time between the two steps is at least 1, 4, 7, 14, 28, 48, or 60 days; or 3, 6 or 9 months; or one year. The expression vector or adenoviral vector comprises a nucleic acid sequence encoding an inhibitor of angiogenesis and a nucleic acid sequence encoding a neurotrophic agent. The nucleic acid sequence encoding the inhibitor of angiogenesis and the nucleic acid sequence encoding the neurotrophic agent are the same nucleic acid sequence. The promoter is a viral promoter, cytomegalovirus immediate early promoter, cellular promoter, an elongation factor 1-oc (EF1-a) promoter, a Ying Yang 1 (Yy1) promoter or an Ubiquitin C (UbC) promoter.

ABEX UPTX: 20040709

ADMINISTRATION - The exogenous material is administered topically, subconjunctivally, retrobulbarly, periocularly, subretinally, suprachoroidally, or intraocularly. It can also be administered orally, intravenously, intraarterially, intramuscularly, subcutaneously, intraperitoneally, parenterally, intranasally, or intratracheally (all claimed).

EXAMPLE - Experimental protocols are described but no results are given.

L61 ANSWER 2 OF 28 WPIX COPYRIGHT 2004 THOMSON DERWENT on STN
AN 2004-388967 [36] WPIX
DNC C2004-145603
TI Use of N-hydroxy acetamide derivatives for treating e.g. age-related macular degeneration, rubeosis iritis, uveitis, retinal ischemia, choroidal vascular insufficiency and choroidal thrombosis.
DC B05
IN BINGAMAN, D P; KLIMKO, P G
PA (ALCO-N) ALCON INC
CYC 103
PI US 2004092558 A1 20040513 (200436)* 8 A61K031-44
WO 2004043352 A2 20040527 (200441) EN A61K000-00
RW: AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HU IE IT LU MC NL PT RO SE SI SK TR
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE EG ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NI NO NZ OM PG PH PL PT RO RU SC SD SE SG SK SL SY TJ TM TN TR TT TZ UA UG US UZ VC VN YU ZA ZM ZW
ADT US 2004092558 A1 **Provisional US 2002-425574P 20021112**, US 2003-697135 20031030; WO 2004043352 A2 WO 2003-US34617 20031030
PRAI **US 2002-425574P 20021112**; US 2003-697135 20031030

IC ICM A61K000-00; A61K031-44
ICS A61K031-19; A61K031-40
AB US2004092558 A UPAB: 20040608
NOVELTY - Treatment of ocular neovascular or edematous diseases or disorders comprises administration of a **histone deacetylase** (HDAC) inhibitor (I).
ACTIVITY - Ophthalmological; Antidiabetic; Antiangiogenic; Vasotropic; Antiinflammatory; Thrombolytic; Vulnerary.
MECHANISM OF ACTION - HDAC inhibitor.
No details of tests for HDAC inhibition activity are given.
USE - (I) are useful for the treatment of ocular neovascular or edematous diseases or disorders (especially diabetic retinopathy, chronic glaucoma, retinal detachment, sickle cell retinopathy, age-related macular degeneration, rubeosis iritis, uveitis, neoplasms, Fuch's heterochromic iridocyclitis, neovascular glaucoma, corneal neovascularization, neovascularization resulting from combined vitrectomy and lensectomy, retinal ischemia, choroidal vascular insufficiency, choroidal thrombosis, carotid artery ischemia, contusive ocular injury, retinopathy of prematurity, retinal vein occlusion, proliferative vitreoretinopathy, corneal angiogenesis, retinal microvasculopathy, and retinal (macular) edema). (claimed)
ADVANTAGE - (I) provide an effective pharmacological therapy for ocular neovascularization and edema thereby avoiding laser photocoagulation or photodynamic therapy (which may cause retinal damage) and invasive surgery, which are the only approved treatments currently available.
Dwg.0/0
FS CPI
FA AB; GI; DCN
MC CPI: B06-H; B07-H; B10-A18; B14-C03; B14-D07; B14-F02D; B14-F02F2; B14-F04; B14-H01B; **B14-N03**; B14-N17B
TECH UPTX: 20040608
TECHNOLOGY FOCUS - PHARMACEUTICALS - Preferred Inhibitor: The HDAC inhibitor is an N-hydroxy acetamide derivative of formula (I).
Y = R1NHC(O) or R2C(O)NR3;
R1, R2, R4 = aryl, heteroaryl, cycloalkyl, heterocycloalkyl, aryloxy, arylalkyloxy, or alkyl (all optionally substituted, with the cyclic systems optionally bicyclic);
R3 = H, alkyl or C(O)R4;
R = (CH2)n or CH(A-R5)-(CH2)n-1;
n = 3-8;
A = NH, O, S, CH2, NHCO or NHCO2; and
R5 = aryl, heteroaryl, cycloalkyl, heterocycloalkyl or alkyl (all optionally substituted, and with the cyclic systems being optionally bicyclic).
ABEX UPTX: 20040608
SPECIFIC COMPOUNDS - The use of 9 compounds (I) is specifically claimed e.g. N-hydroxy-N'-phenyloctanediamide (Ia).

ADMINISTRATION - Dosage of (I) is 0.01-100 mg/kg, administered orally, transdermally, subdermally, intraperitoneally, subcutaneously, transnasally, sublingually or rectally.

L61 ANSWER 3 OF 28 WPIX COPYRIGHT 2004 THOMSON DERWENT on STN
AN 2004-374976 [35] WPIX
DNC C2004-140997
TI Use of **histone deacetylase** inhibitor for the treatment of acute or chronic degenerative conditions or diseases of the eye e.g. glaucoma, retinal ischemia, retinitis pigmentosa and retinopathy.
DC B05
IN HELLBERG, P E
PA (HELL-I) HELLBERG P E; (ALCO-N) ALCON INC
CYC 103

PI US 2004092431 A1 20040513 (200435)* 5 A61K031-00 <--
WO 2004043348 A2 20040527 (200435) EN A61K000-00
RW: AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HU IE IT LU MC NL PT RO SE SI SK TR
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE EG ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NI NO NZ OM PG PH PL PT RO RU SC SD SE SG SK SL SY TJ TM TN TR TT TZ UA UG US UZ VC VN YU ZA ZM ZW

ADT US 2004092431 A1 **Provisional US 2002-425576P 20021112**, US 2003-694309 20031027; WO 2004043348 A2 **WO 2003-US33873 20031027**

PRAI **US 2002-425576P 20021112**; US 2003-694309 20031027

IC ICM A61K000-00; A61K031-00
ICS A61K038-00

AB US2004092431 A UPAB: 20040603
NOVELTY - Treatment of acute or chronic degenerative conditions or diseases of the eye comprises administration of a **histone deacetylase** inhibitor (I).
ACTIVITY - Ophthalmological; Vulnerary; Vasotropic; Antidiabetic; Immunosuppressive.
MECHANISM OF ACTION - **Histone deacetylase** inhibitor. No details of tests for **histone deacetylase** inhibition activity are given.
USE - (I) are useful for the treatment of acute or chronic degenerative conditions or diseases of the eye (preferably glaucoma or dry age-related macular degeneration), retinitis pigmentosa and other forms of heredodegenerative retinal disease, retinal detachment and tears, macular pucker, ischemia affecting the outer retina, cellular damage associated with diabetic retinopathy and retinal ischemia, damage associated with laser therapy (grid, focal, and panretinal) including photodynamic therapy, trauma, surgical (retinal translocation, subretinal surgery, or vitrectomy) or light-induced iatrogenic retinopathy and preservation of retinal transplants (all claimed).
Dwg.0/0

FS CPI
FA AB; DCN
MC CPI: B07-D04C; B10-A08; B10-A18; B14-D07; B14-F02D; **B14-N03**; B14-N17B

ABEX UPTX: 20040603
ADMINISTRATION - Administration of (I) is 0.001-500 (preferably 1-100) mg/day (orally), 0.001-5 (preferably 0.01-2) weight% (topically) or parenteral.

L61 ANSWER 4 OF 28 WPIX COPYRIGHT 2004 THOMSON DERWENT on STN
AN 2004-214406 [20] WPIX
DNC C2004-084902
TI New thienyl-hydroxamic acid derivatives useful as **histone deacetylase** inhibitors for treatment of e.g. cancer, psoriasis, smooth muscle cell proliferation, fungal and parasitic infections.
DC B02 B03
IN ARCHER, J A; BORDOGNA, W; BULL, R J; CLARK, D E; DYKE, H J; GILL, M I A; HARRIS, N V; PRICE, S; VAN DEN HEUVEL, M
PA (ARGE-N) ARGENTA DISCOVERY LTD
CYC 105
PI WO 2004013130 A1 20040212 (200420)* EN 218 C07D409-04
RW: AT BE BG CH CY CZ DE DK EA EE ES FI FR GB GH GM GR HU IE IT KE LS LU MC MW MZ NL OA PT RO SD SE SI SK SL SZ TR TZ UG ZM ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NI NO NZ OM PG PH PL PT RO RU SC SD SE SG SK SL SY TJ TM TN TR TT TZ UA UG US UZ VC VN YU ZA ZM ZW

AU 2003255724 A1 20040223 (200453) C07D409-04
ADT WO 2004013130 A1 WO 2003-GB3168 20030724; AU 2003255724 A1 AU 2003-255724 20030724
FDT AU 2003255724 A1 Based on WO 2004013130
PRAI GB 2003-10462 20030507; **GB 2002-18040 20020802**
IC ICM C07D409-04
ICS A61K031-38; A61P035-00; C07D409-14; C07D413-04; C07D413-14; C07D417-14
AB WO2004013130 A UPAB: 20040324
NOVELTY - Thienyl-hydroxamic acid derivatives (I) and their N-oxides, salts, solvates or prodrugs are new.

DETAILED DESCRIPTION - Thienyl-hydroxamic acid derivatives of formula (I) and their N-oxides, salts, solvates or prodrugs are new.

R1 = aryl or heteroaryl (both optionally substituted by at least one R3, alkylenedioxy, carboxy, CN, halo, OH, NO2, haloalkyl, haloalkoxy, C(O)R3, C(O)OR3, C(=Z)NR4R5, NR4R5, NR6C(O)-OR3, NR6C(O)-NR4R5, NR6C(=Z)R3, OC(O)NR4R5, NR6SO2R3, OR3, OC(O)R3, SH, SR3, SOR3, SO2R3 or SO2NR4R5);

R2 = H, Cl, CN, F, alkoxy, alkyl or haloalkyl;

R3 = aryl, heteroaryl, cycloalkenyl, cycloalkyl, heterocycloalkyl or R7;

R4, R5 = alkyl or alkenyl (all optionally substituted by aryl, heteroaryl, cycloalkenyl, cycloalkyl or heterocycloalkyl), H, aryl, heteroaryl, cycloalkenyl, cycloalkyl or heterocycloalkyl; or

NR4R5 = cyclic amine;

R6 = H or lower alkyl;

R7 = alkyl, alkenyl or alkynyl (all optionally substituted by at least one aryl, heteroaryl, cycloalkenyl, cycloalkyl, heterocycloalkyl, OH, C(=Z)NR4R5, NR4R5, NR6C(=Z)-R8, OC(O)NR4R5, NR6C(O)OR8, NR6C(O)NR4R5, NR6SO2R8, OR8, SOR8, SO2R8 or SO2NR4R5);

R8 = alkyl, alkenyl or alkynyl (all optionally substituted by at least one aryl, heteroaryl, cycloalkenyl, cycloalkyl, heterocycloalkyl, OH or halo), aryl, heteroaryl, cycloalkenyl, cycloalkyl or heterocycloalkyl; and

Z = O or S.

ACTIVITY - Cytostatic; Antipsoriatic; Muscular-Gen.; Antiinflammatory; Immunosuppressive; Neuroprotective; Antiangiogenic; Fungicide; Antiparasitic; Antianemic; Hepatotropic; Antiarteriosclerotic; Vasotropic; Antiarthritic; Antirheumatic; Antidiabetic; Immunosuppressive; Dermatological; Antiallergic; Anticonvulsant; Nootropic; Ophthalmological; Antidiabetic; Protozoacide; Antimalarial; Antisickling; Cardiovascular-Gen.; Cardiant.

MECHANISM OF ACTION - **Histone deacetylase** inhibitor.

In a test using K562 chronic human myelogenous leukemia cells, results showed that 5-(5-((benzofuran-2-ylmethyl)-amino)-pyridin-2-yl)-thiophene-2-carboxylic acid hydroxamide (Ia) exhibited an IC50 value of 0.062 micro M for inhibiting **histone deacetylase** activity.

USE - Used for the treatment of disease caused by increased cell proliferation, cancer, psoriasis, fibroproliferative disorders, smooth muscle cell proliferation disorders, inflammatory diseases and conditions treatable by immune modulation, neurodegenerative disorders, diseases involving angiogenesis, fungal and parasitic infections and hematopoietic disorders, liver fibrosis, arteriosclerosis, restenosis, rheumatoid arthritis, autoimmune diabetes, lupus, allergies, Huntington's disease, retinal diseases (such as diabetic retinopathy, age-related macular degeneration, interstitial keratitis or rubeotic glaucoma), protozoal infections (such as malaria, toxoplasmosis or coccidiosis), anemia, sickle cell anemia, thalassemia and congestive heart failure due to cardiomyocyte hypertrophy (all claimed).

Dwg.0/0

FS CPI
FA AB; GI; DCN
MC CPI: B06-H; B07-F01; B14-A03; B14-A04; B14-B02; B14-C03; B14-C09B; B14-D06; B14-F01B; B14-F01G; B14-F02F1; B14-F02F2; B14-F03; B14-F07; B14-G02A; B14-G02D; B14-G03; B14-H01; B14-J01; B14-J01A4; B14-N12; B14-N13; B14-N17; B14-N17C
TECH UPTX: 20040324
TECHNOLOGY FOCUS - ORGANIC CHEMISTRY - Preparation: Preparation of (I) comprises e.g. reacting an acid compound of formula (II) with O-(tetrahydro-2H-pyran-2-yl)hydroxylamine and a coupling agent such as O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate, in the presence of diisopropylethylamine, in an inert solvent such as dimethylformamide, and reacting the obtained carboxamide compound of formula (III) with an acid catalyst e.g. p-toluene sulfonic acid, in methanol.
ABEX UPTX: 20040324
SPECIFIC COMPOUNDS - 37 Compounds (I) are specifically claimed, e.g. 5-(5-((benzofuran-2-ylmethyl)-amino)-pyridin-2-yl)-thiophene-2-carboxylic acid hydroxamide (Ia).

ADMINISTRATION - The dosage is 0.1-500 mg orally, buccally, intranasally, parenterally, transdermally or rectally, 1-4 times/day.

EXAMPLE - A mixture of 5-(5-aminopyridin-2-yl)-thiophene-2-carboxylic acid methyl ester (55 mg) and benzo(b)furan-2-carboxaldehyde (38 mg), and 4A molecular sieves in anhydrous tetrahydrofuran (3.3 ml), was stirred for 20 hours. Glacial acetic acid (22 ml) and sodium triacetoxyborohydride (108 mg) were then added to the reaction mixture and worked up to give 5-(5-((benzofuran-2-ylmethyl)-amino)-pyridin-2-yl)-thiophene-2-carboxylic acid methyl ester (A). To a solution of (A) (84 mg) in methanol (1.5 ml), and N,N dimethyl acetamide as co-solvent, was added hydroxylamine hydrochloride (64 mg) followed by potassium hydroxide powder (82 mg). After stirring overnight the reaction mixture was diluted with 10% citric acid solution and extracted twice with ethyl acetate. The organic layers were worked up to give 5-(5-((benzofuran-2-ylmethyl)-amino)-pyridin-2-yl)-thiophene-2-carboxylic acid hydroxamide (Ia) (18 mg).

L61 ANSWER 5 OF 28 WPIX COPYRIGHT 2004 THOMSON DERWENT on STN
AN 2004-014494 [02] WPIX
DNC C2004-004714
TI Saccharide uptake promoter for preventing diabetic retinopathy, diabetic nephropathy and diabetic peripheral neuropathy, contains **histone deacetylase** inhibitor.
DC B02
PA (TAIS) TAISHO PHARM CO LTD
CYC 1
PI JP 2003095949 A 20030403 (200402)* 6 A61K031-473
ADT JP 2003095949 A **JP 2001-288223 20010921**
PRAI **JP 2001-288223 20010921**
IC ICM A61K031-473
ICS A61P003-10; A61P043-00
AB JP2003095949 A UPAB: 20040107
NOVELTY - A saccharide uptake promoter contains **histone deacetylase** inhibitor.
DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for:
(1) a pharmaceutical having saccharide uptake promotion effect, which contains compound of formula (I) and its salts; and
(2) a method for promoting the saccharide uptake to the cell, which involves inhibiting the **histone deacetylase.**
R1-R3 = H, halo, 1-6C alkyl, OH, NO2, sulfonyl group, NR5R6 or S(CH2)pR7;
R4 = H, NO2 or sulfonyl group;
n = 4-6;

p = 0-3;
R5, R6 = H or 1-6C alkyl; and
R7 = H, 1-6C alkyl, OH, phenyl or 2-7C alkoxy carbonyl group.
ACTIVITY - Antidiabetic; Nephrotropic; Neuroprotective; Ophthalmological.
MECHANISM OF ACTION - Saccharide Uptake Promoter; **Histone Deacetylase** Inhibitor.
L6 cells were cultivated and culture cell was suspended into a culture medium. 100000 cell was inoculated into a 24 wells plate and the culture solution was exchanged day by day. After 4 days, 1 micro M of the compound (I) was added to a culture solution. HEPES buffer was added to the wells plate and 100 nM of insulin was added. The above culture was incubated at 37 deg. C for 1 hour. The saccharide uptake quantity was measured using labeled 2-deoxyglucose. The result showed that the compound (I) was found to have high saccharide uptake promotion activity compared to control, which does not have compound (I).
USE - For preventing diabetic retinopathy, diabetic nephropathy and diabetic peripheral neuropathy.
ADVANTAGE - The saccharide uptake promoter effectively controls the hyperglycemia in normal blood by promoting the saccharide uptake to the cell.
Dwg.0/2

FS CPI
FA AB; GI; DCN
MC CPI: B06-D13; B14-D06; B14-J01; B14-L01; **B14-N03**; B14-N10; B14-S04

L61 ANSWER 6 OF 28 WPIX COPYRIGHT 2004 THOMSON DERWENT on STN
AN 2003-903558 [82] WPIX
DNC C2003-257001
TI New benzamide derivatives useful for treatment of e.g. cancer, psoriasis, rheumatoid arthritis, atherosclerosis, autoimmune diseases, sepsis and asthma.
DC B02 B03
IN GIBSON, K H; STOKES, E S E; WARING, M J
PA (ASTR) ASTRAZENECA AB; (ASTR) ASTRAZENECA UK LTD
CYC 103
PI WO 2003092686 A1 20031113 (200382)* EN 88 A61K031-44
RW: AT BE BG CH CY CZ DE DK EA EE ES FI FR GB GH GM GR HU IE IT KE LS LU MC MW MZ NL OA PT RO SD SE SI SK SL SZ TR TZ UG ZM ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NI NO NZ OM PH PL PT RO RU SC SD SE SG SK SL TJ TM TN TR TT TZ UA UG US UZ VC VN YU ZA ZM ZW
AU 2003226553 A1 20031117 (200442) A61K031-44
ADT WO 2003092686 A1 WO 2003-GB1703 20030417; AU 2003226553 A1 AU 2003-226553 20030417
FDT AU 2003226553 A1 Based on WO 2003092686
PRAI **GB 2002-9715 20020427**
IC ICM A61K031-44
ICS A61K031-495; A61K031-505; A61P017-06; A61P019-02; A61P019-08; A61P029-00; A61P035-00; C07D239-48; C07D241-26; C07D277-56; C07D401-04
AB WO2003092686 A UPAB: 20031223
NOVELTY - Benzamide derivatives (I) are new.
DETAILED DESCRIPTION - Benzamide derivatives of formula (I), their salts, in vivo hydrolyzable esters and amides, are new.
A = heterocyclyl (optionally substituted on NH by G);
R1 = a substituent on carbon and comprising T1, N,N-(1-6C alkyl)2sulfamoyl, aryl, aryloxy, aryl(1-6C alkyl), heterocyclyl or heterocyclyl(1-6C alkyl) or D-E (all optionally substituted on C by at least one V and optionally heterocyclyl substituted on NH by J);

T1 = halo, nitro, cyano, hydroxy, oxo, trifluoromethyl, trifluoromethoxy, amino, carboxy, carbamoyl, mercapto, sulfamoyl, 1-6C alkyl, 2-6C alkenyl, 2-6C alkynyl, 1-6C alkoxy, 1-6C alkanoyl, 1-6C alkanoyloxy, N-(1-6C alkyl)amino, N,N-(1-6C alkyl)2amino, 1-6C alkanoylamino, N-(1-6C alkyl)carbamoyl, N,N-(1-6C alkyl)2carbamoyl, 1-6C alkylS(O)a, 1-6C alkoxycarbonyl or N-(1-6C alkyl)sulfamoyl;

V = halo, nitro, cyano, OH, oxo, trifluoromethyl, trifluoromethoxy, amino, carboxy, carbamoyl, mercapto, sulfamoyl, 1-6C alkyl, 2-6C alkenyl, 2-6C alkynyl, 1-6C alkoxy, 1-6C alkanoyl, 1-6C alkanoyloxy, N-(1-6C alkyl)amino, N,N-(1-6C alkyl)2amino, 1-6C alkanoylamino, N-(1-6C alkyl)carbamoyl, N,N-(1-6C alkyl)2carbamoyl, 1-6C alkylS(O)a, 1-6C alkoxycarbonyl, N-(1-6C alkyl)sulfamoyl, N,N-(1-6C alkyl)2sulfamoyl or D'-E' (all optionally substituted on C by at least one W);

a = 0-2;

W = T1;

G, J, K = 1-8C alkyl, 2-8C alkenyl, 2-8C alkynyl, 1-8C alkanoyl, 1-8C alkylsulfonyl, 1-8C alkoxycarbonyl, carbamoyl, N-(1-8C alkyl)carbamoyl, N,N-(1-8C alkyl)carbamoyl, benzyloxycarbonyl, benzoyl or phenylsulfonyl, aryl, aryl(1-6C)alkyl or heterocyclyl(1-6C)alkyl (all optionally substituted on C atom by at least one Q);

Q = T1, 1-6C alkoxycarbonylamino, N,N-(1-6C alkyl)2sulfamoyl, aryl, aryloxy, aryl(1-6C alkyl), aryl(1-6C alkoxy), heterocyclyl, heterocyclyl(1-6C alkyl), heterocyclyl(1-6C alkoxy) or Da-Ea (all optionally substituted on C by at least one Z);

Z = T1;

D, D', Da = 1-6C alkyl, 2-6C alkenyl, 2-6C alkynyl, 3-8c cycloalkyl, 3-8C cycloalkyl(1-6C alkyl), aryl, aryl(1-6C alkyl), heterocyclyl or heterocyclyl(1-6C alkyl) (all optionally substituted on C by at least one Fa);

E, E' and Ea = N(Ra), O, C(O)O, OC(O), C(O), N(Ra)C(O), N(Ra)C(O)N(Rb), N(Ra)C(O)O, OC(O)N(Ra), C(O)N(Ra), S(O)r, SO2N(Ra) or N(Ra)SO2;

Ra and Rb = H or 1-6C alkyl (optionally substituted by at least one Fb);

r = 0-2;

Fa, Fb = halo, nitro, cyano, hydroxy, trifluoromethyl, trifluoromethoxy, amino, carboxy, carbamoyl, mercapto, sulfamoyl, 1-6C alkyl, 2-6C alkenyl, 2-6C alkynyl, 1-6C alkoxy, 1-6C alkanoyl, 1-6C alkanoyloxy, N-(1-6C alkyl)amino, N,N-(1-6C alkyl)2amino, 1-6C alkanoylamino, N-(1-6C alkyl)carbamoyl, N,N-(1-6C alkyl)2carbamoyl, 1-6C alkylS(O)a, 1-6C alkoxycarbonyl, N-(1-6C alkyl)sulfamoyl or N,N-(1-6C alkyl)2sulfamoyl;

m = 0-4;

B' = a group of formula (i) or (ii);

X1, X2, Y1-Y4 = CH or N;

R2 = halo;

n, p = 0-2;

R3 = amino or OH, and

R4 = halo, nitro, cyano, hydroxy, trifluoromethyl, trifluoromethoxy, amino, carboxy, carbamoyl, mercapto, sulfamoyl, 1-3C alkyl, 2-3C alkenyl, 2-3C alkynyl, 1-3C alkoxy, 1-3C alkanoyl, 1-3C alkanoyloxy, N-(1-3C alkyl)amino, N,N-(1-3C alkyl)2amino, 1-3C alkanoylamino, N-(1-3C alkyl)carbamoyl, N,N-(1-3C alkyl)2carbamoyl, 1-3C alkylS(O)a, 1-3C alkoxycarbonyl, N-(1-3C alkyl)sulfamoyl or N,N-(1-3C alkyl)2sulfamoyl,

provided that at least one of Y1-Y4 is N.

An INDEPENDENT CLAIM is also included for the preparation of (I).

ACTIVITY - Cytostatic; Anti-HIV; Antipsoriatic; Antirheumatic; Antiarthritic; Antiarteriosclerotic; Vasotropic; Immunosuppressive; Antiinflammatory; Osteopathic; Ophthalmological; Antiallergic; Antigout; Gastrointestinal-Gen.; Antiulcer; Dermatological; Neuroprotective; Antiasthmatic; Respiratory-Gen.; Antibacterial; Hepatotropic; Virucide.

MECHANISM OF ACTION - **Histone deacetylase** inhibitor.

Tests are described, but no results are given.

USE - Used for treatment of cancer (claimed) e.g. Kaposi's sarcoma, psoriasis, rheumatoid arthritis, hemangioma, acute and chronic neuropathies, atheroma, atherosclerosis, arterial restenosis, autoimmune diseases, acute and chronic inflammation, bone diseases, ocular diseases with retinal vessel proliferation, allergic and atopic diseases, inflammatory diseases (e.g. joint inflammation (such as rheumatoid arthritis, osteoarthritis and gout), inflammation of the gastrointestinal tract (such as inflammatory bowel disease, ulcerative colitis and gastritis), and skin inflammation (such as psoriasis, eczema, dermatitis)), multiple sclerosis, spondyloarthropathies (e.g. ankylosing spondylitis, psoriatic arthritis and arthritis connected to ulcerative colitis), AIDS-related neuropathies, system lupus erythematosus, asthma, chronic obstructive lung diseases, bronchitis, pleuritis, adult respiratory distress syndrome, sepsis, and acute and chronic hepatitis (either viral, bacterial or toxic).

ADVANTAGE - (I) Are cell cycle inhibitors, angiogenesis inhibitors and apoptosis activators;

Dwg.0/0

FS CPI

FA AB; GI; DCN

MC CPI: B07-D04; B07-D10; B07-D11; B07-D12; B07-D13; B07-F01; B07-F03; B14-A01; B14-A02; B14-C01; B14-C03; B14-C06; B14-C09; B14-E08; B14-G02; B14-H01B; B14-K01; **B14-N03**; B14-N12; B14-N17

TECH UPTX: 20031223

TECHNOLOGY FOCUS - ORGANIC CHEMISTRY - Preparation (Claimed): Preparation of (I) comprises e.g. reacting an amide compound of formula (II) with a boron compound of formula (III).

X = a reactive group, and

L1, L2 = ligands.

ABEX UPTX: 20031223

ADMINISTRATION - The dosage is 1-50 mg/kg/day orally, parenterally (e.g. intravenously, subcutaneously, intramuscularly or intravascularly), topically or rectally. A unit dosage comprises 5-5000 mg/m2 or 0.1-100 mg/kg or 1-100 (preferably 1-50) mg/kg, of (I). A tablet or capsule comprises 1-250 mg of (I).

EXAMPLE - N2-(2-t-butoxycarbonylaminophenyl)-5-(pyridin-3-yl)thiophene-2-carboxamide (70 mg), 1,4-dioxane (0.67 ml) and a 4M solution of hydrochloric acid in dioxane (0.67 ml) were stirred at ambient temperature for 18 hours. After basic work up, N2-(2-aminophenyl)-5-(pyridin-3-yl)thiophene-2-carboxamide (62%) was obtained.

L61 ANSWER 7 OF 28 WPIX COPYRIGHT 2004 THOMSON DERWENT on STN

AN 2003-902761 [82] WPIX

CR 2003-756805 [71]; 2003-767413 [72]; 2003-779051 [73]; 2003-779052 [73]; 2003-788172 [74]; 2003-788179 [74]; 2003-853537 [79]

DNC C2003-256269

TI New carbonylamino derivatives are inhibitors of **histone deacetylase**, useful for the treatment of e.g. cancer, psoriasis, rheumatoid arthritis, osteoarthritis, atherosclerosis or restenosis.

DC B02 B03

IN BACKX, L J J; VAN BRANDT, S F A; VAN EMELEN, K; VERDONCK, M G C

PA (JANC) JANSSEN PHARM NV

CYC 102

PI WO 2003076395 A1 20030918 (200382)* EN 65 C07C259-10

RW: AT BE BG CH CY CZ DE DK EA EE ES FI FR GB GH GM GR HU IE IT KE LS LU MC MW MZ NL OA PT RO SD SE SI SK SL SZ TR TZ UG ZM ZW

W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT RO RU SC SD SE SG SK SL TJ TM TN TR TT TZ UA UG US UZ VC VN YU ZA ZM ZW

AU 2003212336 A1 20030922 (200431) C07C259-10
ADT WO 2003076395 A1 WO 2003-EP2512 20030311; AU 2003212336 A1 AU 2003-212336 20030311
FDT AU 2003212336 A1 Based on WO 2003076395
PRAI **WO 2002-EP14074 20021210; US 2002-363799P 20020313**
IC ICM C07C259-10
ICS A61K031-4439; A61K031-444; A61K031-4468; A61P029-00; C07D213-78; C07D401-12
AB WO2003076395 A UPAB: 20040514
NOVELTY - Carbonylamino derivatives (I) are new.
DETAILED DESCRIPTION - Carbonylamino derivatives of formula (I) or their N-oxide forms, addition salts and isomeric forms.
n = 0 - 3;
m = 0 - 1;
t = 0 - 4;
Q, X, Y = N or -C=C-;
R1 = e.g. NHC(O)R10;
R10 = H, 1-6C alkyl, 1-6C alkylcarbonyl, aryl(1-6C)aryl, 1-6C alkylpyrazinyl, pyridinone, pyrrolidinone or methylimidazolyl;
R2 = H, halo, OH, amino, nitro, 1-6C alkyl, 1-6C alkyloxy, trifluoromethyl, di(1-6C alkyl)amino, hydroxyamino or naphthalenylsulfonylpyrazinyl;
L = direct bond, 1-6C alkanediyl, 1-6C alkanediyloxy, amino, carbonyl or aminocarbonyl;
R3 = H;
R4 = H, OH, amino, hydroxy(1-6C)alkyl, 1-6C alkyl, 1-6C alkyloxy, aryl(1-6C)alkyl, aminocarbonyl, hydroxycarbonyl, amino(1-6C)alkyl, aminocarbonyl(1-6C)alkyl, hydroxycarbonyl(1-6C)alkyl, hydroxyaminocarbonyl, 1-6C alkyloxycarbonyl, 1-6C alkylamino(1-6C)alkyl or di(1-6C alkyl)amino(1-6C)alkyl;
R5 = H, 1-6C alkyl, 3-10C cycloalkyl, hydroxy(1-6C)alkyl, 1-6C alkyloxy(1-6C)alkyl, di(1-6C alkyl)amino(1-6C alkyl) or aryl;
A = e.g. phenyl (substituted by (R6)s);
s = 0 - 5; and
R6 = e.g. H, halo, OH, amino, nitro, trihalo(1-6C)alkyl, trihalo(1-6C)alkyloxy).
INDEPENDENT CLAIMS are included for the following:
(1) preparation of (I);
(2) detecting or identifying a HDAC (**histone deacetylase**) in a biological sample involving detecting or measuring the formation of a complex between a labeled (I) and HDAC; and
(3) a combination of an anticancer agent and (I).
ACTIVITY - Cytostatic; Antipsoriatic; Antiarthritic; Antirheumatic; Osteopathic; Antigout; Dermatological; Antiinflammatory; Immunosuppressive; Antiarteriosclerotic; Vasotropic; Antiulcer; Antiallergic; Ophthalmological; Antiasthmatic; Antiseborrheic; Antidiabetic; Immunomodulator; Neuroprotective; Respiratory-Gen.; Gynecological; Cardiant; Anti-HIV; Nephrotropic; Antiparkinsonian; Nootropic; Relaxant; Endocrine-Gen.
MECHANISM OF ACTION - HDAC (H2A, H2B, H3 and H4) inhibitors; Smooth muscle cell proliferation inhibitors; Abnormal cell proliferation inhibitors; Apoptosis inducers; Immunosuppressive condition inhibitors; Glyconeogenesis dysfunction inhibitors; Neuromuscular pathology inhibitors; Gene therapy; Tumor growth inhibitors.
HeLa nuclear extracts were incubated at 60 micro g/ml with 2 multiply 10-8 M of radiolabeled peptide substrate (synthetic peptide having 14 - 21 amino acids of histone H4). The substrate was biotinylated at the NH2-terminal part with a 6-aminohexanoic acid spacer and was protected at the COOH-terminal part by an amide group and specifically (3H)acetylated at lysine 16. The substrate, biotin-(6-aminohexanoic)Gly-Ala-((3H)-acetyl-Lys-Arg-His-Arg-Lys-Val-NH2), was added in a buffer containing HEPES (4-(2-hydroxyethyl)-1-piperazine ethane sulfonic acid) (25 mM), sucrose

(1M), bovine serum albumin (BSA) (0.1 mg/ml) and Triton X-100 (RTM) (0.01 %) at pH 7.4. After 30 minutes the deacetylation reaction was terminated. The resulting mixture was incubated with 2-(4-(((naphthalene-2-carbonyl)-amino)-methyl)-piperidin-1-yl)-pyrimidine-5-carboxylic acid hydroxyamide (test compound). The test compound showed pIC50 (the negative log value of the IC50-value) of 8.103.

USE - (I) is used as a medicine and in the manufacture of a medicament for the treatment of proliferative diseases (claimed) e.g. cancer and psoriasis. The cancer includes lung cancer, colon cancer etc. Also useful for the treatment of rheumatoid arthritis, osteoarthritis, juvenile arthritis, gout, polyarthritis, psoriatic arthritis, ankylosing spondylitis, systemic lupus erythematosus, atherosclerosis, restenosis, inflammatory and dermal conditions (e.g. ulcerative colitis, Crohn's disease, allergic rhinitis, graft versus host disease, conjunctivitis, asthma, acute respiratory distress syndrome, Behcet's disease, transplant rejection, urticaria, allergic dermatitis, alopecia areata, scleroderma, exanthema, eczema, dermatomyositis, acne, diabetes, Kawasaki's disease, multiple sclerosis, emphysema, cystic fibrosis and chronic bronchitis), endometriosis, uterine fibroids, disfunctional uterine bleeding endometrial hyperplasia, ocular vascularization (including vasculopathy affecting retinal and choroidal vessels), cardiac dysfunction, HIV infections, renal dysfunction, Parkinson's disease, Alzheimer's disease or neuropathology that results in a cognitive disorder, amyotrophic lateral sclerosis, spinal muscular atrophy and other pathologic conditions amenable to treatment by potentiating expression of a gene; for suppressing endocrine disorders; and for enhancing gene therapy.

ADVANTAGE - (I) shows excellent in vitro HDAC inhibiting enzymatic activity, good metabolic stability, high oral bioavailability and little or no side effects. (I) shows advantageous properties with regard to cellular activity and specific properties with regard to inhibition of cell cycle progression at both G1 and G2 checkpoints (p21 induction capacity). (I) shows valuable diagnostic properties.

Dwg.0/0

FS CPI

FA AB; GI; DCN

MC CPI: B06-H; B07-D05; B14-A02B1; B14-C03; B14-C09; B14-E08; B14-E10C; B14-F01; B14-F02; B14-F03; B14-F07; B14-G02A; B14-G02C; B14-G02D; B14-H01; B14-H01B; B14-J05A; B14-K01A; B14-K01D; B14-K01F; **B14-N03**; B14-N04; B14-N10; B14-N17C; B14-N17D; B14-S01; B14-S04

TECH UPTX: 20031223

TECHNOLOGY FOCUS - ORGANIC CHEMISTRY - Preparation (Claimed): (I) is prepared by reacting an intermediate of formula (II) with an acid such as trifluoroacetic acid to form (I) (in which R1 is C(O)NH(OH)).

ABEX UPTX: 20031223

SPECIFIC COMPOUNDS - 2-(4-(((Naphthalene-2-carbonyl)-amino)-methyl)-piperidin-1-yl)-pyrimidine-5-carboxylic acid hydroxyamide (Ia) is specifically claimed as (I).

ADMINISTRATION - (I) is administered in a dosage of 0.005 - 100 (preferably 0.005 - 10) mg/kg orally, rectally, percutaneously, parenterally or transdermally. A per unit dosage comprises 0.5 - 500 (preferably 10 - 500) mg of (I).

EXAMPLE - Trifluoroacetic acid (0.5 ml) was added at 0 degrees C to a mixture of 2-(4-(((naphthalene-2-carbonyl)-amino)-methyl)-piperidin-1-yl)-pyrimidine-5-carboxylic acid (tetrahydro-pyran-2-yloxy)-amide (0.0006 mol) in methyl alcohol (5 ml). The resulting mixture was then brought to room temperature, then stirred for 48 hours and worked up to form 2-(4-(((naphthalene-2-carbonyl)-amino)-methyl)-piperidin-1-yl)-pyrimidine-5-carboxylic acid hydroxyamide (65 %).

DEFINITIONS - Full Definitions:

n = 0 - 3;

m = 0 - 1;
t = 0 - 4;
Q, X, Y = N or -C=C-;
R1 = C(O)NR8R9, NHC(O)R10, C(O)-1-6C alkanediylSR10, NR11C(O)N(OH)R10, NR11C(O)-1-6C alkanediylSR10, NR11C(O)C=N(OH)R10 or Zn-chelating group;
R8, R9 = H, OH, 1-6C alkyl, hydroxy(1-6C)alkyl, amino(1-6C)alkyl or aminoaryl;
R10 = H, 1-6C alkyl, 1-6C alkylcarbonyl, aryl(1-6C)aryl, 1-6C alkylpyrazinyl, pyridinone, pyrrolidinone or methylimidazolyl;
R11 = H or 1-6C alkyl;
R2 = H, halo, OH, amino, nitro, 1-6C alkyl, 1-6C alkyloxy, trifluoromethyl, di(1-6C alkyl)amino, hydroxyamino or naphthalenylsulfonylpyrazinyl;
L = direct bond, 1-6C alkanediyl, 1-6C alkanediyloxy, amino, carbonyl or aminocarbonyl;
R3 = H;
R4 = H, OH, amino, hydroxy(1-6C)alkyl, 1-6C alkyl, 1-6C alkyloxy, aryl(1-6C)alkyl, aminocarbonyl, hydroxycarbonyl, amino(1-6C)alkyl, aminocarbonyl(1-6C)alkyl, hydroxycarbonyl(1-6C)alkyl, hydroxyaminocarbonyl, 1-6C alkyloxycarbonyl, 1-6C alkylamino(1-6C)alkyl or di(1-6C alkyl)amino(1-6C)alkyl;
R5 = H, 1-6C alkyl, 3-10C cycloalkyl, hydroxy(1-6C)alkyl, 1-6C alkyloxy(1-6C)alkyl, di(1-6C alkyl)amino(1-6C alkyl) or aryl;
A = phenyl (substituted by (R6)s), cyclohexane (substituted by (R6)s), pyridin-2-yl (substituted by (R7)s), pyridin-3-yl (substituted by (R7)s), pyrimidin-2-yl (substituted by (R7)s), piperidin-4-yl (substituted by (R7)s), morpholin-4-yl (substituted by (R7)s), 1H-pyrrol-2-yl (substituted by (R7)s), thiophen-2-yl (substituted by (R7)s), thiophen-3-yl (substituted by (R7)s), furan-2-yl (substituted by (R7)s), isoxazol-4-yl (substituted by (R7)s), isoxazol-5-yl (substituted by (R7)s), 1H-imidazol-4-yl (substituted by (R7)s), 1H-1-lambda-asterisk-4-asterisk-thiazol-4-yl (substituted by (R7)s), thiazolidin-4-yl (substituted by (R7)s), 1H-(1,2,4)trizol-1-yl-C(CH3)2- (substituted by (R7)s), 1,4-phenylene-2,4-dihydro-(1,2,4)triazol-3-on-4-yl (substituted by (R7)s), 1,4-phenylene-yl-isoxazole-4-yl (substituted by (R7)s), naphthalen-2-yl (substituted by (R6)s), naphthalen-1-yl (substituted by (R6)s), quinoline-8-yl (substituted by (R7)s), quinolin-7-yl (substituted by (R7)s), quinoline-3-yl (substituted by (R7)s), (1,6)naphthyridin-2-yl (substituted by (R7)s), 1H-quinolin-2-one-3-yl (substituted by (R7)s), indan-1-yl (substituted by (R6)s), 1H-indol-2-yl (substituted by (R7)s), 1H-inden-2-yl (substituted by (R7)s), 2,3-dihydro-benzofuran-5-yl (substituted by (R7)s), benzothiazol-6-yl (substituted by (R7)s), benzo(1,3)dioxol-5-yl (substituted by (R7)s), 1,3-dihydro-benzoimidazol-2-on-1-yl (substituted by (R7)s), imidazo(2,1-b)thiazol-5-yl (substituted by (R7)s), 4H-pyridazino(1,2-a)pyridazin-1-on-2-yl (substituted by (R7)s), 1H-benzoimidazol-1-yl (substituted by (R7)s), imidazo(1,2-a)pyridin-3-yl (substituted by (R7)s), 3,4-dihydro-1H-quinolin-2-on-6-yl (substituted by (R7)s), quinolin-6-yl (substituted by (R7)s), furan-3-yl (substituted by (R7)s), quinolin-2-yl (substituted by (R7)s), isoquinolin-3-yl(substituted by (R7)s), 1,2,3,4-tetrahydro-naphthalen-6-yl (substituted by (R6)s), pyrrolidin1-yl (substituted by (R7)s), 2,5-dihydro-pyrazolo(3,4-d)pyrimidin-4-on-5-yl (substituted by (R7)s), 3H-thieno(3,2-d)pyrimidin-4-one-3-yl (substituted by (R7)s), 3H-quinazolin-4-on-3-yl (substituted by (R7)s), 1H-indol-5-yl (substituted by (R7)s), dibenzothiophen-4-yl (substituted by (R7)s), dibenzofuran-4-yl (substituted by (R7)s) or piperazin-1-yl (substituted by (R7)s);
s = 0 - 5; and
R6, R7 = H, halo, OH, amino, nitro, trihalo(1-6C)alkyl, trihalo(1-6C)alkyloxy, 1-6C alkyl (optionally substituted with aryl or 3-10C cycloalkyl), 1-6C alkyloxy, 1-6C alkyloxy(1-6C)alkyloxy, 1-6C alkylcarbonyl, 1-6C alkyloxycarbonyl, 1-6C alkylsulfonyl, cyano(1-6C)alkyl, hydroxy(1-6C)alkyl, hydroxy(1-6C)alkyloxy, hydroxy(1-6C)alkylamino, amino(1-6C)alkyloxy, di(1-6C alkyl)aminocarbonyl,

di(hydroxy(1-6C)alkyl)amino, (aryl)(1-6C alkyl)amino, di(1-6C alkyl)amino(1-6C)alkyloxy, di(1-6C alkyl)amino(1-6C alkylamino), di(1-6C alkyl)amino(1-6C)alkylamino(1-6C)alkyl, arylsulfonyl, arylsulfonylamino, aryloxy, aryloxy(1-6C)alkyl, aryl(2-6C)alkenediyl, di(1-6C alkyl)amino, di(1-6C alkyl)amino(1-6C alkyl), di(1-6C alkyl)amino(1-6C alkyl)amino, di(1-6C alkyl)amino(1-6C alkyl)amino(1-6C)alkyl, di(1-6C alkyl)amino(1-6C alkyl)(1-6C alkyl)amino, di(1-6C alkyl)amino(1-6C alkyl)amino(1-6C alkyl)(1-6C alkyl)amino(1-6C alkyl), aminosulfonylamino(1-6C alkyl)amino, aminosulfonylamino(1-6C alkyl)amino(1-6C alkyl), di(1-6C alkyl)aminosulfonylamino(1-6C alkyl)amino, di(1-6C alkyl)aminosulfonylamino(1-6C alkyl)amino(1-6C alkyl), cyano, thiophenyl (optionally substituted with di(1-6C alkyl)amino(1-6C alkyl)amino(1-6C alkyl)(1-6C alkyl)amino(1-6C alkyl), di(1-6C alkyl)amino(1-6C alkyl), 1-6C alkylpiperazinyl(1-6C alkyl), hydroxy(1-6C alkyl)piperazinyl(1-6C alkyl), hydroxy(1-6C alkyloxy)(1-6C alkylpiperazinyl)(1-6C alkyl), di(1-6C alkyl)aminosulfonylpiperazinyl(1-6C)alkyl, 1-6C alkyloxypiperidinyl, 1-6C alkyloxypiperidinyl(1-6C alkyl), morpholinyl(1-6C alkyl), hydroxy(1-6C alkyl)(1-6C alkyl)amino(1-6C alkyl) or di(hydroxy(1-6C alkyl)amino(1-6C alkyl)), furanyl (optionally substituted with hydroxy(1-6C alkyl)), benzofuranyl, imidazolyl, oxazolyl (optionally substituted with aryl or 1-6C alkyl), 1-6C alkyltriazolyl, tetrazolyl, pyrrolidinyl, pyrrolyl, piperidinyl(1-6C)alkyloxy, morpholinyl, 1-6C alkylmorpholinyl, morpholinyl(1-6C)alkyloxy, morpholinyl(1-6C alkyl), morpholinyl(1-6C alkyl)amino, morpholinyl(1-6C alkyl)amino(1-6C alkyl), piperazinyl, 1-6C alkylpiperazinyl, 1-6C alkylpiperazinyl(1-6C alkyloxy), piperazinyl(1-6C alkyl), naphthalenylsulfonylpiperazinyl, naphthalenylsulfonylpiperidinyl, naphthalenylsulfonyl, 1-6C alkylpiperazinyl(1-6C alkyl), 1-6C alkylpiperazinyl(1-6C alkyl)amino, 1-6C alkylpiperazinyl(1-6C alkylamino)(1-6C alkyl), 1-6C alkylpiperazinylsulfonyl, aminosulfonylpiperazinyl(1-6C alkyloxy), aminosulfonylpiperazinyl, aminosulfonylpiperazinyl(1-6C alkyl), di(1-6C alkyl)aminosulfonylpiperazinyl, di(1-6C alkyl)aminosulfonylpiperazinyl(1-6C alkyl), hydroxy(1-6C alkyl)piperazinyl, hydroxy(1-6C alkyl)piperazinyl(1-6C alkyl), 1-6C alkyloxypiperidinyl, 1-6C alkyloxypiperidinyl(1-6C alkyl), piperidinylamino(1-6C alkylamino), piperidinylamino(1-6C alkylamino)(1-6C alkyl), 1-6C alkylpiperidinyl(hydroxy(1-6C alkyl)amino(1-6C alkylamino), 1-6C alkylpiperidinyl(hydroxy(1-6C alkyl)amino(1-6C alkylamino)(1-6C alkyl), hydroxy(1-6C alkyloxy)(1-6C alkylpiperazinyl), hydroxy-1-6C alkyloxy-1-6C alkylpiperazinyl-1-6C alkyl, (hydroxy-1-6C alkyl)(1-6C alkylamino), hydroxy(1-6C alkyl)(1-6C alkyl)amino-1-6C alkyl, hydroxy-1-6C alkylamino-1-6C alkyl, di(hydroxy-1-6C alkyl)amino-1-6C alkyl, pyrrolidinyl(1-6C)alkyl, pyrrolidinyl(1-6C alkyloxy), thiopyrazolyl, pyrazolyl (optionally di-substituted with 1-6C alkyl or trihalo(1-6C alkyl)), pyridinyl (optionally substituted with 1-6C alkyloxy, aryloxy or aryl), pyrimidinyl, tetrahydropyrimidinylpiperazinyl, tetrahydropyrimidinylpiperazinyl(1-6C alkyl), quinolinyl, indole or phenyl (optionally mono- - tri-substituted with halo, amino, nitro, 1-6C alkyl, 1-6C alkyloxy, hydroxy(1-4C alkyl), trifluoromethyl, trifluoromethyloxy, hydroxy(1-4C alkyloxy), 1-4C alkylsulfonyl, 1-4C alkyloxy(1-4C alkyloxy), 1-4C alkyloxycarbonyl, amino(1-4C alkyloxy), di(1-4C alkyl)amino-1-4C alkyloxy, di(1-4C alkyl)amino, di(1-4C alkyl)aminocarbonyl, di(1-4C alkyl)amino(1-4C alkyl), di(1-4C alkyl)amino-1-4C alkylamino(1-4C alkyl), di(1-4C alkyl)amino(1-4C alkyl)amino, di(1-4C alkyl)amino-1-4C alkylamino-1-4C alkyl, di(1-4C alkyl)amino-1-4C alkyl(1-4C alkyl)amino, di(1-4C alkyl)amino-1-4C alkyl(1-4C alkyl)amino-1-4C alkyl, aminosulfonylamino(1-4C alkyl)amino, aminosulfonylamino(1-4C alkyl)amino-1-4C alkyl, di(1-4C alkyl)aminosulfonylamino(1-4C alkyl)amino, di(1-4C alkyl)aminosulfonylamino(1-4C alkyl)amino(1-6C alkyl), cyano, piperidinyl(1-4C alkyloxy), pyrrolidinyl(1-4C alkyloxy), aminosulfonylpiperazinyl, aminosulfonylpiperazinyl(1-4C alkyl), di(1-4C alkyl)aminosulfonylpiperazinyl, di(1-4C alkyl)aminosulfonylpiperazinyl-1-4C alkyl, hydroxy-1-4C alkylpiperazinyl, hydroxy-1-4C alkylpiperazinyl-1-

4C alkyl, 1-4C alkyloxypiperidinyl, 1-4C alkyloxypiperidinyl-1-4C alkyl, hydroxy-1-4C alkyloxy-1-4C alkylpiperazinyl, hydroxy-1-4C alkyloxy-1-4C alkylpiperazinyl-1-4C alkyl, hydroxy-1-4C alkyl-1-4C alkylamino, hydroxy-1-4C alkyl-1-4C alkylamino-1-4C alkyl, di(hydroxy-1-4C alkyl)amino, dihydroxy(1-4C alkyl)amino-1-4C alkyl, furanyl (optionally substituted with -CH=CH-CH=CH-), pyrrolidinyl(1-4C alkyl), pyrrolidinyl(1-4C alkyloxy), morpholinyl, morpholinyl-1-4C alkyloxy, morpholinyl-1-4C alkyl, morpholinyl-1-4C alkylamino, morpholinyl-1-4C alkylamino-1-4C alkyl, piperazinyl, 1-4C alkylpiperazinyl, 1-4C alkylpiperazinyl-1-4C alkyloxy, piperazinyl-1-4C alkyl, 1-4C alkylpiperazinyl-1-4C alkyl, 1-4C alkylpiperazinyl-1-4C alkylamino, 1-4C alkylpiperazinyl-1-4C alkylamino-1-6C alkyl, tetrahydropyrimidinylpiperazinyl, tetrahydropyrimidinylpiperazinyl(1-4C alkyl), piperidinylamino-1-4C alkylamino, piperidinylamino-1-4C alkylamino-1-4C alkyl, (1-4C alkylpiperidinyl)(hydroxy-1-4C alkyl)amino-1-4C alkylamino, (1-4C alkylpiperidinyl)(hydroxy-1-4C alkyl)amino-1-4C alkylamino-1-4C alkyl, pyridinyl-1-4C alkyloxy, hydroxy-1-4C alkylamino, hydroxy-1-4C alkylamino-1-4C alkyl, di(1-4C alkyl)amino-1-4C alkylamino, aminothiadiazolyl, aminosulfonylpiperazinyl-1-4C alkyloxy or thiophenyl-1-4C alkylamino)).

Provided that:

(a) when n is 0, then a direct bond is intended;

(b) when m is 0, then a direct bond is attached to NR5;

(c) when t is 0, then a direct bond is attached to A;

(d) for R3, H-atom is replaced by aryl;

(e) R6 and R7 can be placed on the nitrogen in replacement of the hydrogen; and

(f) aryl is phenyl optionally substituted with at least one halo, 1-6C alkyl, 1-6C alkyloxy, trifluoromethyl, cyano or hydroxycarbonyl.

Preferred Definitions:

n = 1;

m = 0 or 1;

t = 0 - 2;

Q = -C=C-;

R1 = C(O)NH(OH);

R2, R4, R5 = H;

L = direct bond;

A = phenyl (substituted by (R6)s), naphthalen-2-yl (substituted by (R6)s), indan-1-yl (substituted by (R6)s), 1H-indol-2-yl (substituted by (R7)s), 1H-inden-2-yl (substituted by (R7)s) quinolin-2-yl (substituted by (R7)s) or isoquinolin-3-yl(substituted by (R7)s);

s = 0 - 2; and

R6 = H, halo, 1-6C alkyl or 1-6C alkyloxy.

L61 ANSWER 8 OF 28 WPIX COPYRIGHT 2004 THOMSON DERWENT on STN
AN 2003-853537 [79] WPIX
CR 2003-756805 [71]; 2003-767413 [72]; 2003-779051 [73]; 2003-779052 [73]; 2003-788172 [74]; 2003-788179 [74]; 2003-902761 [82]
DNC C2003-240492
TI New piperazinyl-, piperidinyl- or morpholinyl-derivatives useful for the treatment of cancer, psoriasis, rheumatoid arthritis and osteoarthritis.
DC B02 B03
IN VAN EMELEN, K
PA (JANC) JANSSEN PHARM NV
CYC 102
PI WO 2003076438 A1 20030918 (200379)* EN 35 C07D413-04
RW: AT BE BG CH CY CZ DE DK EA EE ES FI FR GB GH GM GR HU IE IT KE LS LU MC MW MZ NL OA PT RO SD SE SI SK SL SZ TR TZ UG ZM ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT RO RU SC SD SE SG SK SL TJ TM TN TR TT TZ UA UG US UZ VC VN YU ZA ZM ZW

AU 2003218735 A1 20030922 (200431) C07D413-04
ADT WO 2003076438 A1 WO 2003-EP2510 20030311; AU 2003218735 A1 AU 2003-218735 20030311
FDT AU 2003218735 A1 Based on WO 2003076438
PRAI **WO 2002-EP14833 20021223; US 2002-363799P 20020313**
IC ICM C07D413-04
ICS A61K031-506; A61P035-00; C07D401-04; C07D403-04
AB WO2003076438 A UPAB: 20040514
NOVELTY - Piperazinyl-, piperidinyl- or morpholinyl-derivatives (I) are new.

DETAILED DESCRIPTION - Piperazinyl-, piperidinyl- or morpholinyl-derivatives of formula (I) or their N-oxide forms, addition salts and isomeric forms.

t = 0 - 4;

Q, X and Y = N or -C=C-;

Z = NH, O or CH2;

R1 = C(O)NR3R4, NHC(O)R7, C(O)-1-6C alkanediylSR7, NR8C(O)N(OH)R7, NR8C(O)-1-6C alkanediylSR7, NR8C(O)C=N(OH)R7 or Zn-chelating group;

R2 - R5 = e.g. H or OH;

R7 and R9 = e.g. H, 1-6C alkyl;

R8 = e.g. H or 1-6C alkyl;

L = e.g. NR9C(O), NR9SO2 or NR9CH2;

A = e.g. phenyl (substituted by (R5)s);

s = 0 - 5.

Full definitions are given in the DEFINITIONS (Full definitions and Preferred definitions) section.

INDEPENDENT CLAIMS are also included for the following:

(1) use of (I) in the manufacture of a medicament for the treatment of proliferative diseases;

(2) preparation of (I);

(3) detecting or identifying a HDAC (**histone deacetylase**) in a biological sample involving detecting or measuring the formation of a complex between a labeled (I) and HDAC; and

(4) a combination of an anticancer agent and (I).

ACTIVITY - Cytostatic; Antipsoriatic; Antiarthritic; Antirheumatic; Osteopathic; Antigout; Dermatological; Antiinflammatory; Immunosuppressive; Antiarteriosclerotic; Vasotropic; Antiulcer; Antiallergic; Ophthalmological; Antiasthmatic; Antiseborrheic; Antidiabetic; Immunomodulator; Neuroprotective; Respiratory-Gen.; Gynecological; Cardiant; Anti-HIV; Nephrotropic; Antiparkinsonian; Nootropic; Relaxant; Endocrine Gen.

MECHANISM OF ACTION - HADC (H2A, H2B, H3 and H4) inhibitors; Smooth muscle cell proliferation inhibitors; Abnormal cell proliferation inhibitors; Apoptosis inducers; Immunosuppressive condition inhibitors; glyconeogenesis dysfunction inhibitors; Neuromuscular pathology inhibitors; Gene therapy; Tumor growth inhibitors.

HeLa nuclear extracts were incubated at 60 micro g/ml with 2 multiply 10-8 M of radiolabeled peptide substrate (synthetic peptide having 14 - 21 amino acids of histone H4). The substrate was biotinylated at the NH2-terminal part with a 6-aminohexanoic acid spacer and was protected at the COOH-terminal part by an amide group and specifically (3H)acetylated at lysine 16. The substrate, biotin-(6-aminohexanoic)Gly-Ala-((3H)-acetyl-Lys-Arg-His-Arg-Lys-Val-NH2), was added in a buffer containing Hepes (25 mM), sucrose (1M), BSA (0.1 mg/ml) and Triton X-100 (RTM) (0.01%) at pH 7.4. After 30 minutes the deacetylation reaction was terminated. The resulting mixture was incubated with 2-(2-((biphenyl-4-sulfonylamino)-methyl)-morpholin-4-yl)-pyrimidine-5-carboxylic acid hydroxyamide (test compound). The test compound showed pIC50 (the negative log value of the IC50-value) of 8.097.

USE - As a medicine and in the manufacture of a medicament for the treatment of proliferative diseases (claimed) e.g. cancer and psoriasis. The cancer includes lung cancer, colon cancer etc. Also useful for the

treatment of rheumatoid arthritis, osteoarthritis, juvenile arthritis, gout, polyarthritis, psoriatic arthritis, ankylosing spondylitis, systemic lupus erythematosus, atherosclerosis, restenosis, inflammatory and dermal conditions (e.g. ulcerative colitis, Crohn's disease, allergic rhinitis, graft versus host disease, conjunctivitis, asthma, acute respiratory distress syndrome, Behcet's disease, transplant rejection, urticaria, allergic dermatitis, alopecia areata, scleroderma, exanthema, eczema, dermatomyositis, acne, diabetes, Kawasaki's disease, multiple sclerosis, emphysema, cystic fibrosis and chronic bronchitis), endometriosis, uterine fibroids, disfunctional uterine bleeding endometrial hyperplasia, ocular vascularization (including vasculopathy affecting retinal and choroidal vessels), cardiac dysfunction, HIV infections, renal dysfunction, Parkinson's disease, Alzheimer's disease or neuropathology that results in a cognitive disorder, amyotrophic lateral sclerosis, spinal muscular atrophy and other pathologic conditions amenable to treatment by potentiating expression of a gene; for suppressing endocrine disorders; and for enhancing gene therapy.

ADVANTAGE - (I) shows excellent in vitro HADC inhibiting enzymatic activity, good metabolic stability, high oral bioavailability and little or no side effects. (I) shows advantageous properties with regard to cellular activity and specific properties with regard to inhibition of cell cycle progression at both G1 and G2 checkpoints (p21 induction capacity). (I) shows valuable diagnostic properties.

Dwg.0/0

FS CPI

FA AB; GI; DCN

MC CPI: B07-H; B14-A02B1; B14-C06; B14-C09A; B14-C09B; B14-E10C; B14-F01B; B14-F01G; B14-F07; B14-G02C; B14-H01; B14-J01A3; B14-J01A4; B14-K01; B14-K01A; **B14-N03**; B14-N04; B14-N10; B14-N14; B14-N17; B14-S01

TECH UPTX: 20031208

TECHNOLOGY FOCUS - ORGANIC CHEMISTRY - Preparation (Claimed): (I) is prepared by reacting an intermediate of formula (II) with an acid such as trifluoroacetic acid to form (I) (in which R1 is C(O)NH(OH)).

ABEX UPTX: 20031208

SPECIFIC COMPOUNDS - 7 Compounds are specifically claimed as (I) e.g. 2-(2-((biphenyl-4-sulfonylamino)-methyl)-morpholin-4-yl)-pyrimidine-5-carboxylic acid hydroxyamide (IA).

ADMINISTRATION - (I) is administered in a dosage of 0.005 - 100 (preferably 0.005 - 10) mg/kg orally, rectally, percutaneously, parenterally or transdermally. A per unit dosage comprises 0.5 - 500 (preferably 10 - 500) mg of (I).

EXAMPLE - A mixture of 2-(2-((biphenyl-4-sulfonylamino)-methyl)-morpholin-4-yl)-pyrimidine-5-carboxylic acid ethyl ester (0.0004 mol) and sodium hydroxide (0.0008 ml) in ethyl alcohol (10 ml) was stirred at 80degreesC for 48 hours, then cooled to room temperature. The resulting mixture was then subjected to basic work up to form 2-(2-((biphenyl-4-sulfonylamino)-methyl)-morpholin-4-yl)-pyrimidine-5-carboxylic acid hydroxyamide (64%).

DEFINITIONS - Full Definitions:

t = 0 - 4;

Q, X and Y = N or -C=C-;

Z = NH, O or CH2;

R1 = C(O)NR3R4, NHC(O)R7, C(O)-1-6C alkanediylSR7, NR8C(O)N(OH)R7, NR8C(O)-1-6C alkanediylSR7, NR8C(O)C=N(OH)R7 or Zn-chelating group;

R3 and R4 = H, OH, 1-6C alkyl, hydroxy(1-6C)alkyl, amino(1-6C)alkyl or aminoaryl;

R7 = H, 1-6C alkyl, 1-6C alkylcarbonyl, aryl(1-6C)aryl, 1-6C alkylpyrazinyl, pyridinone, pyrrolidinone or methylimidazolyl;

R8 = H or 1-6C alkyl;

R2 = H, OH, amino, hydroxy(1-6C)alkyl, 1-6C alkyl, 1-6C alkyloxy, aryl(1-6C)alkyl, aminocarbonyl, hydroxycarbonyl, amino(1-6C)alkyl,

aminocarbonyl(1-6C)alkyl, hydroxycarbonyl(1-6C)alkyl, hydroxyaminocarbonyl, 1-6C alkyloxycarbonyl, 1-6C alkylamino(1-6C)alkyl or di(1-6C alkyl)amino(1-6C)alkyl;
L = bivalent radical selected from -NR9C(O)-, -NR9SO2- or -NR9CH2-;
R9 = H, 1-6C alkyl, 3-10C cycloalkyl, hydroxy(1-6C) alkyl, 1-6C alkyloxy(1-6C)alkyl or di(1-6C alkyl)amino(1-6C)alkyl;
A = phenyl (substituted by (R5)s), cyclohexane (substituted by (R5)s), pyridin-2-yl (substituted by (R6)s), pyridin-3-yl (substituted by (R6)s), pyrimidin-2-yl (substituted by (R6)s), piperidin-4-yl (substituted by (R6)s), morpholin-4-yl (substituted by (R6)s), 1H-pyrrol-2-yl (substituted by (R6)s), thiophen-2-yl (substituted by (R6)s), thiophen-3-yl (substituted by (R6)s), furan-2-yl (substituted by (R6)s), isoxazol-4-yl (substituted by (R6)s), isoxazol-5-yl (substituted by (R6)s), 1H-imidazol-4-yl (substituted by (R6)s), 1H-1lambdaasterisk4asterisk-thiazol-4-yl (substituted by (R6)s), thiazolidin-4-yl (substituted by (R6)s), 1H-(1,2,4)trizol-1-yl-C(CH3)2- (substituted by (R6)s), 1,4-phenylene-2,4-dihydro-(1,2,4)triazol -3-on-4-yl (substituted by (R6)s), 1,4-phenylene-yl-isoxazole-4-yl (substituted by (R6)s), naphthalen-2-yl (substituted by (R6)s), naphthalen-1-yl (substituted by (R6)s), quinoline-8-yl (substituted by (R6)s), quinolin-7-yl (substituted by (R6)s), quinoline-3-yl (substituted by (R6)s), (1,6)naphthyridin-2-yl (substituted by (R6)s), 1H-quinolin-2-one-3-yl (substituted by (R6)s), indan-1-yl (substituted by (R5)s), 1H-indol-2-yl (substituted by (R6)s), 1H-inden-2-yl (substituted by (R6)s), 2,3-dihydro-benzofuran-5-yl (substituted by (R6)s), benzothiazol-6-yl (substituted by (R6)s), benzo(1,3)dioxol-5-yl (substituted by (R6)s), 1,3-dihydro-benzoimidazol-2-on-1-yl (substituted by (R6)s), imidazo(2,1-b)thiazol-5-yl (substituted by (R6)s), 4H-pyridazino(1,2-a)pyridazin-1-on-2-yl (substituted by (R6)s), 1H-benzoimidazol-1-yl (substituted by (R6)s), imidazo(1,2-a)pyridin-3-yl (substituted by (R6)s), 3,4-dihydro-1H-quinolin-2-on-6-yl (substituted by (R6)s), quinolin-6-yl (substituted by (R6)s), furan-3-yl (substituted by (R6)s), quinolin-2-yl (substituted by (R6)s), isoquinolin-3-yl(substituted by (R6)s), 1,2,3,4-tetrahydro-naphthalen-6-yl (substituted by (R5)s), pyrrolidin1-yl (substituted by (R6)s), 2,5-dihydro-pyrazolo(3,4-d)pyrimidin-4-on-5-yl (substituted by (R6)s), 3H-thieno(3,2-d)pyrimidin-4-one-3-yl (substituted by (R6)s), 3H-quinazolin-4-on-3-yl (substituted by (R6)s), 1H-indol-5-yl (substituted by (R6)s), dibenzothiophen-4-yl (substituted by (R6)s), dibenzofuran-4-yl (substituted by (R6)s) or piperazin-1-yl (substituted by (R6)s);
s = 0 - 5;
R5 and R6 = H, halo, OH, nitro, trihalo(1-6C)alkyl, trihalo(1-6C)alkyloxy, 1-6C alkyl (optionally substituted with aryl or 3-10C cycloalkyl), 1-6C alkyloxy, 1-6C alkyloxy(1-6C)alkyloxy, 1-6C alkylcarbonyl, 1-6C alkyloxycarbonyl, 1-6C alkylsulfonyl, cyano(1-6C)alkyl, hydroxy(1-6C)alkyl, hydroxy(1-6C)alkyloxy, hydroxy(1-6C)alkylamino, amino(1-6C)alkyloxy, di(1-6C alkyl)aminocarbonyl, di(hydroxy(1-6C)alkyl)amino, (aryl)(1-6C alkyl)amino, di(1-6C alkyl)amino(1-6C)alkyloxy, di(1-6C alkyl)amino(1-6C alkylamino), di(1-6C alkyl)amino(1-6C)alkylamino(1-6C)alkyl, arylsulfonyl, arylsulfonylamino, aryloxy, aryloxy(1-6C)alkyl, aryl(2-6C)alkenediyl, di(1-6C alkyl)amino, di(1-6C alkyl)amino(1-6C alkyl), di(1-6C alkyl)amino(1-6C alkyl)amino, di(1-6C alkyl)amino(1-6C alkyl)amino(1-6C)alkyl, di(1-6C alkyl)amino(1-6C alkyl)(1-6C alkyl)amino, di(1-6C alkyl)amino(1-6C alkyl)(1-6C alkyl)amino(1-6C alkyl), aminosulfonylamino(1-6C alkyl)amino, aminosulfonylamino(1-6C alkyl)amino(1-6C alkyl), di(1-6C alkyl)aminosulfonylamino(1-6C alkyl)amino, di(1-6C alkyl)aminosulfonylamino(1-6C alkyl)amino(1-6C alkyl), cyano, thiophenyl (optionally substituted with di(1-6C alkyl)amino(1-6C alkyl)(1-6C alkyl)amino(1-6C alkyl), di(1-6C alkyl)amino(1-6C alkyl), 1-6C alkylpiperazinyl(1-6C alkyl), hydroxy(1-6C alkyl)piperazinyl(1-6C alkyl), hydroxy(1-6C alkyloxy)(1-6C alkylpiperazinyl)(1-6C alkyl), di(1-6C alkyl)aminosulfonylpiperazinyl(1-6C)alkyl, 1-6C alkyloxypiperidinyl, 1-6C alkyloxypiperidinyl(1-6C alkyl), morpholinyl(1-6C alkyl), hydroxy(1-6C

alkyl)(1-6C alkyl)amino(1-6C alkyl) or di(hydroxy(1-6C alkyl)amino(1-6C alkyl)), furanyl (optionally substituted with hydroxy(1-6C alkyl)), benzofuranyl, imidazolyl, oxazolyl (optionally substituted with aryl or 1-6C alkyl), 1-6C alkyltriazolyl, tetrazolyl, pyrrolidinyl, pyrrolyl, piperidinyl(1-6C)alkyloxy, morpholinyl, 1-6C alkylmorpholinyl, morpholinyl(1-6C)alkyloxy, morpholinyl(1-6C alkyl), morpholinyl(1-6C alkyl)amino, morpholinyl(1-6C alkyl)amino(1-6C alkyl), piperazinyl, 1-6C alkylpiperazinyl, 1-6C alkylpiperazinyl(1-6C alkyloxy, piperazinyl(1-6C alkyl), naphthalenylsulfonylpiperazinyl, naphthalenylsulfonylpiperidinyl, naphthalenylsulfonyl, 1-6C alkylpiperazinyl(1-6C alkyl), 1-6C alkylpiperazinyl(1-6C alkyl)amino, 1-6C alkylpiperazinyl(1-6C alkylamino)(1-6C alkyl), 1-6C alkylpiperazinylsulfonyl, aminosulfonylpiperazinyl(1-6C alkyloxy), aminosulfonylpiperazinyl, aminosulfonylpiperazinyl(1-6C alkyl), di(1-6C alkyl)aminosulfonylpiperazinyl, di(1-6C alkyl)aminosulfonylpiperazinyl(1-6C alkyl), hydroxy(1-6C alkyl)piperazinyl, hydroxy(1-6C alkyl)piperazinyl(1-6C alkyl), 1-6C alkyloxypiperidinyl, 1-6C alkyloxypiperdinyl(1-6C alkyl), piperidinylamino(1-6C alkylamino), piperidinylamino(1-6C alkylamino)(1-6C alkyl), 1-6C alkylpiperidinyl(hydroxy(1-6C alkyl)amino(1-6C alkylamino), (1-6C alkylpiperidinyl)(hydroxy(1-6C alkyl)amino(1-6C alkylamino)(1-6C alkyl), hydroxy(1-6C alkyloxy)(1-6C alkylpiperazinyl), hydroxy-1-6C alkyloxy-1-6C alkylpiperazinyl-1-6C alkyl, (hydroxy-1-6C alkyl)(1-6C alkylamino), hydroxy(1-6C alkyl)(1-6C alkyl)amino-1-6C alkyl, hydroxy-1-6C alkylamino-1-6C alkyl, di(hydroxy-1-6C alkyl)amino-1-6C alkyl, pyrrolidinyl(1-6C)alkyl, pyrrolidinyl(1-6C alkyloxy), thiopyrazolyl, pyrazolyl (optionally di-substituted with 1-6C alkyl or trihalo(1-6C alkyl)), pyridinyl (optionally substituted with 1-6C alkyloxy, aryloxy or aryl), pyrimidinyl, tetrahydropyrimidinylpiperazinyl, tetrahydropyrimidinylpiperazinyl(1-6C alkyl), quinolinyl, indole or phenyl (optionally mono- - tri-substituted with halo, amino, nitro, 1-6C alkyl, 1-6C alkyloxy, hydroxy(1-4C alkyl), trifluoromethyl, trifluoromethyloxy, hydroxy(1-4C alkyloxy), 1-4C alkylsulfonyl, 1-4C alkyloxy(1-4C alkyloxy), 1-4C alkyloxycarbonyl, amino(1-4C alkyloxy), di(1-4C alkyl)amino-1-4C alkyloxy, di(1-4C alkyl)amino, di(1-4C alkyl)aminocarbonyl, di(1-4C alkyl)amino(1-4C alkyl), di(1-4C alkyl)amino-1-4C alkylamino(1-4C alkyl), di(1-4C alkyl)amino(1-4C alkyl)amino, di(1-4C alkyl)amino(1-4C alkyl)amino-1-4C alkyl, di(1-4C alkyl)amino-1-4C alkyl(1-4C alkyl)amino, di(1-4C alkyl)amino-1-4C alkyl(1-4C alkyl)amino-1-4C alkyl, aminosulfonylamino(1-4C alkyl)amino, aminosulfonylamino(1-4C alkyl)amino-1-4C alkyl, di(1-4C alkyl)aminosulfonylamino(1-4C alkyl)amino, di(1-4C alkyl)aminosulfonylamino(1-4C alkyl)amino(1-6C alkyl), cyano, piperidinyl(1-4C alkyloxy), pyrrolidinyl(1-4C alkyloxy), aminosulfonylpiperazinyl, aminosulfonylpiperazinyl(1-4C alkyl), di(1-4C alkyl)aminosulfonylpiperazinyl, di(1-4C alkyl)aminosulfonylpiperazinyl-1-4C alkyl, hydroxy-1-4C alkylpiperazinyl, hydroxy-1-4C alkylpiperazinyl-1-4C alkyl, 1-4C alkyloxypiperidinyl, 1-4C alkyloxypiperidinyl-1-4C alkyl, hydroxy-1-4C alkyloxy-1-4C alkylpiperazinyl, hydroxy-1-4C alkyloxy-1-4C alkylpiperazinyl-1-4C alkyl, (hyroxy-1-4C alkyl)(1-4C alkyl)amino, hydroxy-1-4C alkyl-(1-4C alkyl)amino-1-4C alkyl, hydroxy-1-4C alkylamino-1-4C alkyl, di(hydroxy-1-4C alkyl)amino-1-4C alkyl, furanyl (optionally substituted with -CH=CH-CH=CH-), pyrrolidinyl(1-4C alkyl), pyrrolidinyl(1-4C alkyloxy), morpholinyl, morpholinyl-1-4C alkyloxy, morpholinyl-1-4C alkyl, morpholinyl-1-4C alkylamino, morpholinyl-1-4C alkylamino-1-4C alkyl, piperazinyl, 1-4C alkylpiperazinyl, 1-4C alkylpiperazinyl-1-4C alkyloxy, piperazinyl-1-4C alkyl, 1-4C alkylpiperazinyl-1-4C alkyl, 1-4C alkylpiperazinyl-1-4C alkylamino, 1-4C alkylpiperazinyl-1-4C alkylamino-1-6C alkyl, pyrimidinylpiperazinyl, pyrimidinylpiperazinyl-1-4C alkyl, piperidinylamino-1-4C alkylamino, piperidinylamino-1-4C alkylamino-1-4C alkyl, (1-4C alkylpiperidinyl)(hydroxy-1-4C alkyl)amino-1-4C alkylamino, (1-4C alkylpiperidinyl)(hydroxy-1-4C alkyl)amino-1-4C alkylamino-1-4C alkyl, pyridinyl-1-4C alkyloxy, hydroxy-1-4C alkylamino, di(hydroxy-1-4C

alkyl)amino, di(1-4C alkyl)amino-1-4C alkylamino, aminothiadiazolyl, aminosulfonylpiperazinyl-1-4C alkyloxy or thiophenyl-1-4C alkylamino).
Provided that:
(a) when t is 0, then a direct bond is attached to L;
(b) R5 and R6 is replaced on the nitrogen atom in replacement of H; and
(c) aryl is phenyl optionally substituted with at least one halo, 1-6C alkyl, 1-6C alkyloxy, trifluoromethyl, cyano or hydroxycarbonyl.
Preferred Definitions:
t = 1;
Q = -C=C-;
X and Y = N;
Z = O or CH2;
R1 = C(O)NH(OH);
R2 = H;
L = NHC(O) or NHSO2;
A = phenyl (substituted by (R5)s), or naphthalene-2-yl (substituted by (R5)s);
s = 0 or 1;
R5 = H or phenyl.

L61 ANSWER 9 OF 28 WPIX COPYRIGHT 2004 THOMSON DERWENT on STN
AN 2003-833524 [77] WPIX
DNC C2003-234496
TI New carbamic acid compounds useful for treating e.g. cancer, proliferative disorders and psoriasis, comprising piperazine linkage.
DC B02 B03 C02
IN DIKOVSKA, K; FINN, P W; GAILITE, V; KALVINSH, R; LOLYA, D; LOZA, E; RITCHIE, J; ROMERO-MARTIN, M; STARCHENKOV, I; WATKINS, C J; KALVINSH, I
PA (PROL-N) PROLIFIX LTD
CYC 103
PI WO 2003082288 A1 20031009 (200377)* EN 109 A61K031-495
RW: AT BE BG CH CY CZ DE DK EA EE ES FI FR GB GH GM GR HU IE IT KE LS LU MC MW MZ NL OA PT RO SD SE SI SK SL SZ TR TZ UG ZM ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NI NO NZ OM PH PL PT RO RU SC SD SE SG SK SL TJ TM TN TR TT TZ UA UG US UZ VC VN YU ZA ZM ZW
AU 2003229883 A1 20031013 (200435) A61K031-495
ADT WO 2003082288 A1 WO 2003-GB1463 20030403; AU 2003229883 A1 AU 2003-229883 20030403
FDT AU 2003229883 A1 Based on WO 2003082288
PRAI **US 2002-369337P 20020403**
IC ICM A61K031-495
ICS A61K031-496; C07D209-20; C07D239-42; C07D295-18; C07D295-22; C07D317-58; C07D333-60
AB WO2003082288 A UPAB: 20031128
NOVELTY - Carbamic acid compounds (I) containing a piperazine linkage, their salts, solvates, amides, ester, ether, chemically protected forms or prodrugs are new.
DETAILED DESCRIPTION - Carbamic acid compounds of formula (I) containing a piperazine linkage, their salts, solvates, amides, ester, ether, chemically protected forms or prodrugs are new.
T = cyclyl group selected from 3-20C carbocyclyl, 3-20C heterocyclyl or 5-20C aryl (all optionally substituted);
Q1 = 1-7C alkylene, 1-7C alkylene-X-1-7C alkylene, -X-1-7C alkylene or 1-7C alkylene-X- (all optionally substituted) or a covalent bond;
X = -O- or -S-;
A = optionally substituted piperazin-1,4-diyl group;
Q2 = acid linker group selected from 4-8C alkylene, 5-20C arylene, 5-20C arylene-1-7C alkylene or 1-7C alkylene-5-20C arylene-1-7C alkylene (all optionally substituted and having a backbone length of at least 4 atoms);

J1 = bond or -C(O)-; and
J2 = -C(O)- or -S(O)2-.

ACTIVITY - Cytostatic; Antipsoriatic; Antiarteriosclerotic; Vasotropic; Nootropic; Neuroprotective; Antiparkinsonian; Anticonvulsant; Antiinflammatory; Osteopathic; Antiarthritic; Antirheumatic; Antiangiogenic; Antidiabetic; Ophthalmological; Antianemic; Fungicide; Antiparasitic; Virucide; Immunosuppressive; Dermatological; Antiallergic; Antiasthmatic; Hepatotropic.

MECHANISM OF ACTION - **Histone deacetylase** (HDAC) inhibitor; Cell proliferation regulator; Cell cycle progression inhibitor; Apoptosis promoter.

A source of HDAC (crude HeLa extract (2 micro l)) was incubated with radioactively labelled peptide along (3 micro l) along with dilution of (E)-N-hydroxy-3-(3-((4-(2-pyridinyl)-1-piperazinyl)sulfonyl)phenyl)-2-propenamide (Ib) (1.5 micro l) in a buffer (20 mM Tris pH 7.4, 10% glycerol). The reaction was carried out at 37 deg. C for 1 hour and the reaction was stopped. Then ethyl acetate (750 micro l) was added, the samples were vortexed and after centrifugation, 600 micro l from the upper phase was transferred to a vial containing scintillation fluid (3 ml). The radioactivity was determined and HDAC inhibition was calculated. The % inhibition of HDAC using (Ib) was 600% at 100 nM.

USE - In the manufacture of a medicament for treating a condition mediated by **histone deacetylase** (HDAC) of the human or animal body by therapy, e.g. proliferative condition, cancer and psoriasis (claimed), fibroproliferative disorders (e.g. liver fibrosis), smooth muscle proliferative disorder (e.g. atherosclerosis, restenosis), neurodegenerative diseases (e.g. Alzheimer's disease, Parkinson's disease, Huntington's chorea, amyotropic lateral sclerosis and spino-cerebellar degeneration), inflammatory disease (e.g. osteoarthritis, rheumatoid arthritis), diseases involving angiogenesis (e.g. diabetic retinopathy), hematopoietic disorders (e.g. anemia, sickle cell anemia, thalassemia), fungal infection, parasitic infection, viral infection, conditions treatable by immune modulation (e.g. multiple sclerosis, autoimmune disease, lupus, atopic dermatitis, allergies, asthma, allergic rhinitis, inflammatory bowel disease, and for improving grafting of transplants).

ADVANTAGE - The compounds are potent inhibitors of **histone deacetylase.** The compounds regulate cell proliferation, inhibit cell cycle progression and promote apoptosis.

Dwg.0/0

FS CPI

FA AB; GI; DCN

MC CPI: B06-H; B07-D11; B14-A02; B14-A04; B14-B02; B14-C03; B14-C09; B14-D08; B14-E10C; B14-F01G; B14-F03; B14-F07; B14-G02A; B14-G02C; B14-G02D; B14-G03; B14-H01; B14-H03; B14-J01; B14-J07; B14-K01A; **B14-N03**; B14-N04; B14-N12; B14-N16; B14-N17; B14-S01; B14-S04; C06-H; C07-D11; C14-A02; C14-A04; C14-B02; C14-C03; C14-C09; C14-D08; C14-E10C; C14-F01G; C14-F03; C14-F07; C14-G02A; C14-G02C; C14-G02D; C14-G03; C14-H01; C14-H03; C14-J01; C14-J07; C14-K01A; **C14-N03**; C14-N04; C14-N12; C14-N16; C14-N17; C14-S01; C14-S04

TECH UPTX: 20031128

TECHNOLOGY FOCUS - ORGANIC CHEMISTRY - Preparation: Carbamic acid compounds of formula (Ia) are prepared by:
(1) reacting chloro sulfonate of formula (II) with a piperazine compound of formula (III) to form piperazine sulfonamide ester of formula (IV); and
(2) converting (IV) to (Ia), by hydrolysis with NaOH, reaction with (COCl2), followed by reaction with NH2OH.
NB: R is not defined.

ABEX UPTX: 20031128

WIDER DISCLOSURE - Also disclosed are new intermediates in the preparation of (I).

SPECIFIC COMPOUNDS - 81 Compounds (I) are specifically claimed, e.g. (E)-N-hydroxy-3-(3-((4-(2-pyridinyl)-1-piperazinyl)sulfonyl)phenyl)-2-

propenamide (Ib).

ADMINISTRATION - The dosage of (I) is 0.1 - 250 mg/kg/day and administered orally, buccally, sublingually, transdermally, transmucosally, intranasally, ocularly, pulmonarily, rectally, vaginally, parenterally (e.g. subcutaneously, intradermally, intramuscularly, intravenously, intraarterially, intracardiacally, intrathecally, intraspinally, intracapsularly, subcapsularly, intraorbitally, intraperitoneally, intratracheally, subcuticularly, intraarticularly, subarachnoidally, or intrasternally), or by implantation.

EXAMPLE - To a suspension of hydroxylamine hydrochloride (0.27 g) in tetrahydrofuran (6 ml) a saturated NaHCO3 solution (6.9 ml) was added and the resultant mixture was stirred at ambient temperature for 10 minutes. To the reaction mixture (E)-3-(3-((4-(2-pyridinyl)-1-piperazinyl)sulfonyl)phenyl)-2-propenoyl chloride (ca. 0.78 mmol) solution in tetrahydrofuran (4 ml) was added and the obtained mixture was stirred at ambient temperature for one hour. The organic layer was separated, the water layer was supplemented with water (ca. 5 ml) and extracted with ethyl acetate. After work up (E)-N-hydroxy-3-(3-((4-(2-pyridinyl)-1-piperazinyl)sulfonyl)phenyl)-2-propenamide (Ib) (yield 63%) was obtained.

DEFINITIONS - Preferred Definitions:
Q1 = 1-3C alkylene, 1-3C alkylene-X-1-3C alkylene or 1-3C alkylene-X- (all optionally substituted by halo, OH, -OMe, -OEt, -OPr, Ph, -NH2, -CONH2 or =O) or covalent bond;
Q2 = methylene-phenylene, ethylene-phenylene, phenylene-methylene, phenylene-ethylene, phenylene-ethenylene, methylene-phenylene-methylene, methylene-phenylene-ethylene, methylene-phenylene-ethenylene, ethylene-phenylene-methylene, ethylene-phenylene-ethylene, ethylene-phenylene-ethenylene (all optionally substituted; and having a backbone of at least 4 atoms; where phenylene linkage is para or meta), -C(O)OMe, -C(O)OEt, -C(O)O(Pr), -C(O)O(iPr), -C(O)O(nBu), -C(O)O(sec-Bu), -C(O)O(iso-Bu), -C(O)O(tert-Bu), -C(O)O(n-pentyl), -C(O)OCH2CH2OH, -C(O)OCH2CH2OMe, -C(O)OCH2CH2OEt, -(C=O)NH2, -(C=O)NMe2, -(C=O)NEt2, -(CO)N(iPr)2, -(C=O)N(CH2CH2OH)2, -(C=O)Me, -(C=O)Et, -(C=O)-cHex, -(C=O)Ph, halo, -OH, -OMe, -OEt, -O(iso-Pr), -O(tert-Bu), -OPh, -OCF3, -OCH2CF3, -OCH2CH2OH, -OCH2CH2OMe, -OCH2CH2OEt, -OCH2CH2NH2, -OCH2CH2NMe2, -OCH2CH2N(iso-Pr)2, -OPh-Me, -OPh-OH, -OPh-OMe, -O-Ph-F, -OPh-Cl, -OPh-Br, -OPh-I, -Me, -Et, -nPr, -isoPr, -nBu, -iso-Bu, -sec-Bu, -tert-Bu, -nPe, CF3, -CH2CF3, -CH2CH2OH, -CH2CH2OMe, -CH2CH2OEt, -CH2CH2NH2, -CH2CH2NMe2, -CH2CH2N(iPr)2, -CH2-Ph, -Ph, -Ph-Me, -Ph-OH, -Ph-OMe, -Ph-F, -Ph-Cl, -Ph-Br, -Ph-I, -SO2Me, -SO2Et, -SO2Ph, -SO2NH2, -SO2NMe2, -SO2Net2, -NMe2, -Net2, morpholine, -NO2, -CN or -(CH2)5-8-; and
T = phenyl (optionally substituted by 1-7C alkyl or 5-20C aryl (both optionally substituted), ester, amido, acyl, halo, hydroxyl, ether, sulfonyl, sulfonamide, amino, morpholino, nitro or cyano).

L61 ANSWER 10 OF 28 WPIX COPYRIGHT 2004 THOMSON DERWENT on STN
AN 2003-788179 [74] WPIX
CR 2003-756805 [71]; 2003-767413 [72]; 2003-779051 [73]; 2003-779052 [73]; 2003-788172 [74]; 2003-853537 [79]; 2003-902761 [82]
DNC C2003-217599
TI New sulfonyl derivatives useful for the treatment of proliferative diseases e.g. cancer, psoriasis, asthma, arthritis, systemic lupus erythematosus, atherosclerosis, multiple sclerosis, Crohn's disease and Behcet's disease.
DC B02 B03
IN ARTS, J; BACKX, L J J; DE WINTER, H L J; DYATKIN, A B; MEERPOEL, L; PILATTE, I N C; PONCELET, V S; VAN BRANDT, S F A; VAN EMELEN, K; VERDONCK, M G C
PA (JANC) JANSSEN PHARM NV
CYC 102

PI WO 2003076422 A1 20030918 (200374)* EN 69 C07D295-22
RW: AT BE BG CH CY CZ DE DK EA EE ES FI FR GB GH GM GR HU IE IT KE LS LU MC MW MZ NL OA PT RO SD SE SI SK SL SZ TR TZ UG ZM ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT RO RU SC SD SE SG SK SL TJ TM TN TR TT TZ UA UG US UZ VC VN YU ZA ZM ZW
AU 2003218738 A1 20030922 (200431) C07D295-22
ADT WO 2003076422 A1 WO 2003-EP2516 20030311; AU 2003218738 A1 AU 2003-218738 20030311
FDT AU 2003218738 A1 Based on WO 2003076422
PRAI **US 2002-420989P 20021024; US 2002-363799P 20020313**
IC ICM C07D295-22
ICS C07D207-28; C07D213-82; C07D215-36; C07D233-84; C07D239-42; C07D241-24; C07D261-10; C07D307-79; C07D333-34; C07D403-12; C07D409-04; C07D409-12; C07D413-12; C07D513-04

AB WO2003076422 A UPAB: 20040514
NOVELTY - Heterocyclic sulfonyl derivatives (I) are new.
DETAILED DESCRIPTION - Heterocyclic sulfonyl derivatives of formula (I) or their N-oxide forms, addition salts and isomeric forms are new.
T1 = a group of formula (i);
n = 0 - 3;
t = 0 - 4;
Q, X, Y' = N or C;
R1 = e.g. NHC(O)R9;
R9 = H, 1-6C alkyl, 1-6C alkylcarbonyl, aryl(1-6C)aryl, 1-6C alkylpyrazinyl, pyridinone, pyrrolidinone or methylimidazolyl;
R2 = H, halo, OH, amino, nitro, 1-6C alkyl, 1-6C alkyloxy, trifluoromethyl, di(1-6C alkyl)amino, hydroxyamino or naphthalenylsulfonylpyrazinyl;
L' = direct bond, 1-6C alkanediyl, 1-6C alkanediyloxy, amino, carbonyl or aminocarbonyl;
R3 = H;
A = e.g. phenyl (substituted by (R5)s);
s = 0-5; and
R5 = e.g. H, halo, OH, amino, nitro, trihalo(1-6C)alkyl).
Z' = N or CH; and
R4 = H, OH, amino, hydroxy(1-6C)alkyl, 1-6C alkyl, 1-6C alkyloxy, aryl(1-6C)alkyl, aminocarbonyl, hydroxycarbonyl, amino(1-6C)alkyl, aminocarbonyl(1-6C)alkyl, hydroxycarbonyl(1-6C)alkyl, hydroxyaminocarbonyl, 1-6C alkyloxycarbonyl, 1-6C alkylamino(1-6C)alkyl or di(1-6C alkyl)amino(1-6C)alkyl.
Full definitions are given in the DEFINITIONS (Full definitions and Preferred definitions) section. INDEPENDENT CLAIMS are included for the following:
(1) use of (I) in the manufacture of a medicament for the treatment of proliferative diseases;
(2) preparation of (I);
(3) detecting or identifying a HDAC (**histone deacetylase**) in a biological sample involving detecting or measuring the formation of a complex between a labeled (I) and HDAC; and
(4) a combination of an anticancer agent and (I).
ACTIVITY - Cytostatic; Antipsoriatic; Antiarthritic; Antirheumatic; Osteopathic; Antigout; Dermatological; Antiinflammatory; Immunosuppressive; Antiarteriosclerotic; Vasotropic; Antiulcer; Antiallergic; Ophthalmological; Antiasthmatic; Antiseborrheic; Antidiabetic; Immunomodulator; Hemostatic; Neuroprotective; Respiratory-Gen.; CNS-Gen.; Gynecological; Cardiant; Anti-HIV; Nephrotropic; Antiparkinsonian; Muscular-Gen.; Gastrointestinal-Gen.; Endocrine-Gen.; Nootropic.
MECHANISM OF ACTION - HDAC (H2A, H2B, H3 and H4) inhibitors;

Apoptosis inducers; Gene therapy.

HeLa nuclear extracts were incubated at 60 mu g/ml with 2 multiply 10-8 M of radiolabeled peptide substrate (synthetic peptide having 14 - 21 amino acids of histone H4). The substrate was biotinylated at the NH2-terminal part with a 6-aminohexanoic acid spacer and was protected at the COOH-terminal part by an amide group and specifically (3H)acetylated at lysine 16. The substrate, biotin-(6-aminohexanoic)Gly-Ala-((3H)-acetyl-Lys-Arg-His-Arg-Lys-Val-NH2), was added in a buffer containing Hepes (25 mM), sucrose (1M), BSA (0.1 mg/ml) and Triton X-100 (RTM) (0.01%) at pH 7.4. After 30 minutes the deacetylation reaction was terminated. The resulting mixture was incubated with 2-(4-(2'-(4-methyl-piperazin-1-ylmethyl)-biphenyl-4-sulfonyl)-piperazin-1-yl)-pyrimidine-5-carboxylic acid hydroxyamide (test compound). The test compound showed pIC50 (the negative log value of the IC50-value) of 8.869.

USE - (I) Are useful as a medicine and in the manufacture of a medicament for the treatment of proliferative diseases (claimed) such as psoriasis and cancer e.g. lung cancer, colon cancer and leukemia. Also useful for the treatment of rheumatoid arthritis, osteoarthritis, juvenile arthritis, gout, polyarthritis, psoriatic arthritis, ankylosing spondylitis, systemic lupus erythematosus, atherosclerosis, restenosis, inflammatory and dermal conditions (e.g. ulcerative colitis, Crohn's disease, allergic rhinitis, graft versus host disease, conjunctivitis, asthma, acute respiratory distress syndrome, Behcet's disease, transplant rejection, urticaria, allergic dermatitis, alopecia areata, scleroderma, exanthema, eczema, dermatomyositis, acne, diabetes, Kawasaki's disease, multiple sclerosis, emphysema, cystic fibrosis and chronic bronchitis), endometriosis, uterine fibroids, dysfunctional uterine bleeding endometrial hyperplasia, ocular vascularization (including vasculopathy affecting retinal and choroidal vessels), cardiac dysfunction, HIV infections, renal dysfunction, Parkinson's disease, Alzheimer's disease or neuropathology that results in a cognitive disorder, amyotrophic lateral sclerosis, spinal muscular atrophy and other pathologic conditions amenable to treatment by potentiating expression of a gene; for suppressing endocrine disorders; and for enhancing gene therapy.

ADVANTAGE - (I) Shows excellent in vitro HADC inhibiting enzymatic activity, good metabolic stability, high oral bioavailability and little or no side effects. (I) shows advantageous properties with regard to cellular activity and specific properties with regard to inhibition of cell cycle progression at both G1 and G2 checkpoints (p21 induction capacity). (I) shows valuable diagnostic properties. Moreover, (I) has low affinity for the P450 enzymes, which reduce the risk of adverse drug-drug interaction allowing also for a wider safety margin.

Dwg.0/0

FS CPI

FA AB; GI; DCN

MC CPI: B05-A03B; B06-A03; B06-E05; B06-H; B07-A01; B07-B01; B07-D03; B07-D11; B07-D12; B07-H; B11-C07B; B11-C08; B11-C10; B12-K04E; B14-A02B1; B14-C02; B14-C03; B14-C04; B14-C06; B14-D01; B14-D02; B14-D07A; B14-E10C; B14-F01; B14-F07; B14-F08; B14-G02; B14-H01; B14-H03; B14-J01A3; B14-J01A4; B14-J05; B14-K01; **B14-N03**; B14-N04; B14-N06B; B14-N10; B14-N14; B14-N17; B14-R02; B14-S01; B14-S04; N02-F01; N07-B

TECH UPTX: 20031117

TECHNOLOGY FOCUS - ORGANIC CHEMISTRY - Preparation (Claimed): The sulfonyl derivatives (I) are prepared by:

(a) Reacting an intermediate of formula (II) with an acid (preferably trifluoroacetic acid) to form (I) (in which R1 is C(O)NH(OH)); or

(b) Catalytic hydrogenation of an intermediate of formula (VI) with hydrogen in the presence of a catalyst such as palladium on carbon (10%) to form (I) (in which R1 is C(O)NH(OH)); or

(c) Reacting an intermediate of formula (VII) with an intermediate of formula R'-C(O)OH (VIII) in the presence of N'-(ethylcarbonimidoyl)-N,N-dimethyl-1,3-propanediamine, monohydrochloride and hydroxybenzotriazole to

form (I) (in which R1 is -NH-C(O)-1-methyl-1H-imidazol-4-yl, -NH-C(O)-1H-pyridin-2-one-5-yl, -NH-C(O)-5-methyl-pyrazin-2-yl, -NH-C(O)-pyrrolidin-2-one-5-yl or -NH-C(O)-1H-pyridin-2-one-3-yl). R' = 1-methyl-1H-imidazol-4-yl, 1H-pyridin-2-one-5-yl, 5-methyl-pyrazin-2-yl, pyrrolidin-2-one-5-yl or 1H-pyridin-2-one-3-yl.

ABEX UPTX: 20031117

SPECIFIC COMPOUNDS - 20 Compounds are specifically claimed as (I) e.g. 2-(4-(2'-(4-methyl-piperazin-1-ylmethyl)-biphenyl-4-sulfonyl)-piperazin-1-yl)-pyrimidine-5-carboxylic acid hydroxyamide (Ia).

ADMINISTRATION - (I) Is administered in a dosage of 0.005 - 100 (preferably 0.005 - 10) mg/kg orally, rectally, percutaneously, parenterally or transdermally. A per unit dosage comprises 0.5 - 500 (preferably 10 - 500) mg of (I).

EXAMPLE - Trifluoroacetic acid (4 ml) was added at 0 degrees C to a solution of 2-(4-(2-naphthalenylsulfonyl)-1-piperazinyl)-N-((tetrahydro-2H-pyran-2-yl)oxy)-5-pyrimidinecarboxamide (0.0005 mol) in methyl alcohol (20 ml). The mixture was stirred at room temperature for 48 hours. The resulting reaction mixture was then worked up to give 2-(4-(naphthalene-2-sulfonyl)-piperazin-1-yl)-pyrimidine-5-carboxylic acid hydroxyamide (83%).

DEFINITIONS - Full Definitions:

T1 = a group of formula (i) which is optionally bridged (forming a bicyclic moiety) with a methylene, ethylene or propylene group;

n = 0-3;

t = 0-4;

Q, X, Y' = N or C;

Z' = N or CH;

R1 = C(O)NR7R8, NHC(O)R9, C(O)-1-6C alkanediylSR9, NR10C(O)N(OH)R9, NR10C(O)-1-6C alkanediylSR9, NR10C(O)C=N(OH)R9 or Zn-chelating group;

R7, R8 = H, OH, 1-6C alkyl, hydroxy(1-6C)alkyl, amino(1-6C)alkyl or aminoaryl;

R9 = H, 1-6C alkyl, 1-6C alkylcarbonyl, aryl(1-6C)aryl, 1-6C alkylpyrazinyl, pyridinone, pyrrolidinone or methylimidazolyl;

R10 = H or 1-6C alkyl;

R2 = H, halo, OH, amino, nitro, 1-6C alkyl, 1-6C alkyloxy, trifluoromethyl, di(1-6C alkyl)amino, hydroxyamino or naphthalenylsulfonylpyrazinyl;

L' = direct bond, 1-6C alkanediyl, 1-6C alkanediyloxy, amino, carbonyl or aminocarbonyl;

R3 = H;

R4 = H, OH, amino, hydroxy(1-6C)alkyl, 1-6C alkyl, 1-6C alkyloxy, aryl(1-6C)alkyl, aminocarbonyl, hydroxycarbonyl, amino(1-6C)alkyl, aminocarbonyl(1-6C)alkyl, hydroxycarbonyl(1-6C)alkyl, hydroxyaminocarbonyl, 1-6C alkyloxycarbonyl, 1-6C alkylamino(1-6C)alkyl or di(1-6C alkyl)amino(1-6C)alkyl;

A = phenyl (substituted by (R5)s), cyclohexane (substituted by (R5)s), pyridin-2-yl (substituted by (R6)s), pyridin-3-yl (substituted by (R6)s), pyrimidin-2-yl (substituted by (R6)s), piperidin-4-yl (substituted by (R6)s), morpholin-4-yl (substituted by (R6)s), 1H-pyrrol-2-yl (substituted by (R6)s), thiophen-2-yl (substituted by (R6)s), thiophen-3-yl (substituted by (R6)s), furan-2-yl (substituted by (R6)s), isoxazol-4-yl (substituted by (R6)s), isoxazol-5-yl (substituted by (R6)s), 1H-imidazol-4-yl (substituted by (R6)s), 1H-1lambdaasterisk4asterisk-thiazol-4-yl (substituted by (R6)s), thiazolidin-4-yl (substituted by (R6)s), 1H-(1,2,4)trizol-1-yl-C(CH3)2- (substituted by (R6)s), 1,4-phenylene-2,4-dihydro-(1,2,4)triazol -3-on-4-yl (substituted by (R6)s), 1,4-phenylene-yl-isoxazole-4-yl (substituted by (R6)s), naphthalen-2-yl (substituted by (R6)s), naphthalen-1-yl (substituted by (R6)s), quinoline-8-yl (substituted by (R6)s), quinolin-7-yl (substituted by (R6)s), quinoline-3-yl (substituted by (R6)s), (1,6)naphthyridin-2-yl (substituted by (R6)s), 1H-quinolin-2-one-3-yl (substituted by (R6)s), indan-1-yl (substituted by (R5)s), 1H-indol-2-yl (substituted by (R6)s), 1H-inden-2-yl (substituted by (R6)s), 2,3-dihydro-benzofuran-5-yl

(substituted by (R6)s), benzothiazol-6-yl (substituted by (R6)s), benzo(1,3)dioxol-5-yl (substituted by (R6)s), 1,3-dihydro-benzoimidazol-2-on-1-yl (substituted by (R6)s), imidazo(2,1-b)thiazol-5-yl (substituted by (R6)s), 4H-pyridazino(1,2-a)pyridazin-1-on-2-yl (substituted by (R6)s), 1H-benzoimidazol-1-yl (substituted by (R6)s), imidazo(1,2-a)pyridin-3-yl (substituted by (R6)s), 3,4-dihydro-1H-quinolin-2-on-6-yl (substituted by (R6)s), quinolin-6-yl (substituted by (R6)s), furan-3-yl (substituted by (R6)s), quinolin-2-yl (substituted by (R6)s), isoquinolin-3-yl(substituted by (R6)s), 1,2,3,4-tetrahydro-naphthalen-6-yl (substituted by (R5)s), pyrrolidin1-yl (substituted by (R6)s), 2,5-dihydro-pyrazolo(3,4-d)pyrimidin-4-on-5-yl (substituted by (R6)s), 3H-thieno(3,2-d)pyrimidin-4-one-3-yl (substituted by (R6)s), 3H-quinazolin-4-on-3-yl (substituted by (R6)s), 1H-indol-5-yl (substituted by (R6)s), dibenzothiophen-4-yl (substituted by (R6)s), dibenzofuran-4-yl (substituted by (R6)s) or piperazin-1-yl (substituted by (R6)s);
s = 0-5;
R5, R6 = H, halo, OH, amino, nitro, trihalo(1-6C)alkyl, trihalo(1-6C)alkyloxy, 1-6C alkyl (optionally substituted with aryl or 3-10C cycloalkyl), 1-6C alkyloxy, 1-6C alkyloxy(1-6C)alkyloxy, 1-6C alkylcarbonyl, 1-6C alkyloxycarbonyl, 1-6C alkylsulfonyl, cyano(1-6C)alkyl, hydroxy(1-6C)alkyl, hydroxy(1-6C)alkyloxy, hydroxy(1-6C)alkylamino, amino(1-6C)alkyloxy, di(1-6C alkyl)aminocarbonyl, di(hydroxy(1-6C)alkyl)amino, (aryl)(1-6C alkyl)amino, di(1-6C alkyl)amino(1-6C alkyloxy, di(1-6C alkyl)amino(1-6C alkylamino), di(1-6C alkyl)amino(1-6C)alkylamino(1-6C)alkyl, arylsulfonyl, arylsulfonylamino, aryloxy, aryloxy(1-6C)alkyl, aryl(2-6C)alkenediyl, di(1-6C alkyl)amino, di(1-6C alkyl)amino(1-6C alkyl), di(1-6C alkyl)amino(1-6C alkyl)amino, di(1-6C alkyl)amino(1-6C alkyl)amino(1-6C)alkyl, di(1-6C alkyl)amino(1-6C alkyl)(1-6C alkyl)amino, di(1-6C alkyl)amino(1-6C alkyl)(1-6C alkyl)amino(1-6C alkyl), aminosulfonylamino(1-6C alkyl)amino, aminosulfonylamino(1-6C alkyl)amino(1-6C alkyl), di(1-6C alkyl)aminosulfonylamino(1-6C alkyl)amino, di(1-6C alkyl)aminosulfonylamino(1-6C alkyl)amino(1-6C alkyl), cyano, thiophenyl (optionally substituted with di(1-6C alkyl)amino(1-6C alkyl)(1-6C alkyl)amino(1-6C alkyl), di(1-6C alkyl)amino(1-6C alkyl), 1-6C alkylpiperazinyl(1-6C alkyl), hydroxy(1-6C alkyl)piperazinyl(1-6C alkyl), hydroxy(1-6C alkyloxy)(1-6C alkylpiperazinyl)(1-6C alkyl), di(1-6C alkyl)aminosulfonylpiperazinyl(1-6C)alkyl, 1-6C alkyloxypiperidinyl, 1-6C alkyloxypiperidinyl(1-6C alkyl), morpholinyl(1-6C alkyl), hydroxy(1-6C alkyl)(1-6C alkyl)amino(1-6C alkyl) or di(hydroxy(1-6C alkyl)amino(1-6C alkyl)), furanyl (optionally substituted with hydroxy(1-6C alkyl)), benzofuranyl, imidazolyl, oxazolyl (optionally substituted with aryl or 1-6C alkyl), 1-6C alkyltriazolyl, tetrazolyl, pyrrolidinyl, pyrrolyl, piperidinyl(1-6C)alkyloxy, morpholinyl, 1-6C alkylmorpholinyl, morpholinyl(1-6C)alkyloxy, morpholinyl(1-6C alkyl), morpholinyl(1-6C alkyl)amino, morpholinyl(1-6C alkyl)amino(1-6C alkyl), piperazinyl, 1-6C alkylpiperazinyl, 1-6C alkylpiperazinyl(1-6C alkyloxy), piperazinyl(1-6C alkyl), naphthalenylsulfonylpiperazinyl, naphthalenylsulfonylpiperidinyl, naphthalenylsulfonyl, 1-6C alkylpiperazinyl(1-6C alkyl), 1-6C alkylpiperazinyl(1-6C alkyl)amino, 1-6C alkylpiperazinyl(1-6C alkylamino)(1-6C alkyl), 1-6C alkylpiperazinylsulfonyl, aminosulfonylpiperazinyl(1-6C alkyloxy), aminosulfonylpiperazinyl, aminosulfonylpiperazinyl(1-6C alkyl), di(1-6C alkyl)aminosulfonylpiperazinyl, di(1-6C alkyl)aminosulfonylpiperazinyl(1-6C alkyl), hydroxy(1-6C alkyl)piperazinyl, hydroxy(1-6C alkyl)piperazinyl(1-6C alkyl), 1-6C alkyloxypiperidinyl, 1-6C alkyloxypiperidinyl(1-6C alkyl), piperidinylamino(1-6C alkylamino), piperidinylamino(1-6C alkylamino)(1-6C alkyl), 1-6C alkylpiperidinyl(hydroxy(1-6C alkyl)amino(1-6C alkylamino), 1-6C alkylpiperidinyl(hydroxy(1-6C alkyl)amino(1-6C alkylamino)(1-6C alkyl), hydroxy(1-6C alkyloxy)(1-6C alkylpiperazinyl), hydroxy-1-6C alkyloxy-1-6C alkylpiperazinyl-1-6C alkyl, (hydroxy-1-6C alkyl)(1-6C alkylamino), hydroxy(1-6C alkyl)(1-6C alkyl)amino-1-6C alkyl, hydroxy-1-6C

alkylamino-1-6C alkyl, di(hydroxy-1-6C alkyl)amino-1-6C alkyl, pyrrolidinyl(1-6C)alkyl, pyrrolidinyl(1-6C alkyloxy), thiopyrazolyl, pyrazolyl (optionally di-substituted with 1-6C alkyl or trihalo(1-6C alkyl)), pyridinyl (optionally substituted with 1-6C alkyloxy, aryloxy or aryl), pyrimidinyl, tetrahydropyrimidinylpiperazinyl, tetrahydropyrimidinylpiperazinyl(1-6C alkyl), quinolinyl, indole or phenyl (optionally mono- - tri-substituted with halo, amino, nitro, 1-6C alkyl, 1-6C alkyloxy, hydroxy(1-4C alkyl), trifluoromethyl, trifluoromethyloxy, hydroxy(1-4C alkyloxy), 1-4C alkylsulfonyl, 1-4C alkyloxy(1-4C alkyloxy), 1-4C alkyloxycarbonyl, amino(1-4C alkyloxy), di(1-4C alkyl)amino-1-4C alkyloxy, di(1-4C alkyl)amino, di(1-4C alkyl)aminocarbonyl, di(1-4C alkyl)amino(1-4C alkyl), di(1-4C alkyl)amino-1-4C alkylamino(1-4C alkyl), di(1-4C alkyl)amino(1-4C alkyl)amino, di(1-4C alkyl)amino-1-4C alkylamino-1-4C alkyl, di(1-4C alkyl)amino-1-4C alkyl(1-4C alkyl)amino, di(1-4C alkyl)amino-1-4C alkyl(1-4C alkyl)amino-1-4C alkyl, aminosulfonylamino(1-4C alkyl)amino, aminosulfonylamino(1-4C alkyl)amino-1-4C alkyl, di(1-4C alkyl)aminosulfonylamino(1-4C alkyl)amino, di(1-4C alkyl)aminosulfonylamino(1-4C alkyl)amino(1-6C alkyl), cyano, piperidinyl(1-4C alkyloxy), pyrrolidinyl(1-4C alkyloxy), aminosulfonylpiperazinyl, aminosulfonylpiperazinyl(1-4C alkyl), di(1-4C alkyl)aminosulfonylpiperazinyl, di(1-4C alkyl)aminosulfonylpiperazinyl-1-4C alkyl, hydroxy-1-4C alkylpiperazinyl, hydroxy-1-4C alkylpiperazinyl-1-4C alkyl, 1-4C alkyloxypiperidinyl, 1-4C alkyloxypiperidinyl-1-4C alkyl, hydroxy-1-4C alkyloxy-1-4C alkylpiperazinyl, hydroxy-1-4C alkyloxy-1-4C alkylpiperazinyl-1-4C alkyl, hydroxy-1-4C alkyl-1-4C alkylamino, hydroxy-1-4C alkyl-1-4C alkylamino-1-4C alkyl, di(hydroxy-1-4C alkyl)amino, dihydroxy(1-4C alkyl)amino-1-4C alkyl, furanyl (optionally substituted with -CH=CH-CH=CH-), pyrrolidinyl(1-4C alkyl), pyrrolidinyl(1-4C alkyloxy), morpholinyl, morpholinyl-1-4C alkyloxy, morpholinyl-1-4C alkyl, morpholinyl-1-4C alkylamino, morpholinyl-1-4C alkylamino-1-4C alkyl, piperazinyl, 1-4C alkylpiperazinyl, 1-4C alkylpiperazinyl-1-4C alkyloxy, piperazinyl-1-4C alkyl, 1-4C alkylpiperazinyl-1-4C alkyl, 1-4C alkylpiperazinyl-1-4C alkylamino, 1-4C alkylpiperazinyl-1-4C alkylamino-1-6C alkyl, tetrahydropyrimidinylpiperazinyl, tetrahydropyrimidinylpiperazinyl(1-4C alkyl), piperidinylamino-1-4C alkylamino, piperidinylamino-1-4C alkylamino-1-4C alkyl, (1-4C alkylpiperidinyl)(hydroxy-1-4C alkyl)amino-1-4C alkylamino, (1-4C alkylpiperidinyl)(hydroxy-1-4C alkyl)amino-1-4C alkylamino-1-4C alkyl, pyridinyl-1-4C alkyloxy, hydroxy-1-4C alkylamino, hydroxy-1-4C alkylamino-1-4C alkyl, di(1-4C alkyl)amino-1-4C alkylamino, aminothiadiazolyl, aminosulfonylpiperazinyl-1-4C alkyloxy or thiophenyl-1-4C alkylamino)).

Where aryl is phenyl optionally substituted with at least one halo, 1-6C alkyl, 1-6C alkyloxy, trifluoromethyl, cyano or hydroxycarbonyl. Provided that:

(a) when n is 0, then a direct bond is attached to Z;

(b) when t is 0, then a direct bond is attached to A;

(c) R5 and R6 can be placed on the nitrogen in replacement of the hydrogen; and

(d) for R3, H-atom can be replaced by aryl.

Preferred Definitions:

n = 1;

t = 0;

Z' = N;

R1 = C(O)NH(OH);

R2 = H;

L' = direct bond;

R3, R4 = H;

A = phenyl (substituted by (R5)s) or naphthalen-2-yl (substituted by (R5)s);

s = 0 or 1; and

R5 = H, thiophenyl (optionally substituted with di(1-6C alkyl)amino(1-6C alkyl) or 1-6C alkylpiperazinyl(1-6C alkyl)), furanyl or phenyl

(optionally substituted with di(1-4C alkyl)amino(1-4C alkyloxy), di(1-4C alkyl)amino, di(1-4C alkyl)amino(1-4C alkyl), di(1-4C alkyl)amino(1-4C alkyl(1-4C alkyl)amino(1-4C alkyl), pyrrolidinyl(1-4C alkyl), pyrrolidinyl(1-4C alkyloxy) or 1-4C alkylpiperazinyl(1-4C alkyl).

L61 ANSWER 11 OF 28 WPIX COPYRIGHT 2004 THOMSON DERWENT on STN
AN 2003-788172 [74] WPIX
CR 2003-756805 [71]; 2003-767413 [72]; 2003-779051 [73]; 2003-779052 [73]; 2003-788179 [74]; 2003-853537 [79]; 2003-902761 [82]
DNC C2003-217593
TI New heterocyclic **histone deacetylase** inhibitor compounds useful for treating e.g. cancer, psoriasis, gout, arthritis, systemic lupus erythematosus, atherosclerosis, Crohn's disease, diabetes, cystic fibrosis and asthma.
DC B03
IN ANGIBAUD, P R; DYATKIN, A B; MEERPOEL, L; VAN BRANDT, S F A; VAN EMELEN, K; VERDONCK, M G C
PA (JANC) JANSSEN PHARM NV
CYC 102
PI WO 2003075929 A1 20030918 (200374)* EN 26 A61K031-505
RW: AT BE BG CH CY CZ DE DK EA EE ES FI FR GB GH GM GR HU IE IT KE LS LU MC MW MZ NL OA PT RO SD SE SI SK SL SZ TR TZ UG ZM ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT RO RU SC SD SE SG SK SL TJ TM TN TR TT TZ UA UG US UZ VC VN YU ZA ZM ZW
AU 2003218737 A1 20030922 (200431) A61K031-505
ADT WO 2003075929 A1 WO 2003-EP2515 20030311; AU 2003218737 A1 AU 2003-218737 20030311
FDT AU 2003218737 A1 Based on WO 2003075929
PRAI **US 2002-363799P 20020313**
IC ICM A61K031-505
ICS A61P035-00; C07D207-09; C07D217-02; C07D239-42; C07D295-14; C07D307-68; C07D401-04; C07D401-12; C07D471-10; C12Q001-34
AB WO2003075929 A UPAB: 20040514
NOVELTY - Heterocyclic **histone deacetylase** inhibitor compounds (I), their N-oxide forms, salts or isomeric forms are new.
DETAILED DESCRIPTION - Heterocyclic **histone deacetylase** inhibitor compounds of formula (I), their N-oxide forms, salts or isomeric forms are new.
n = 0-3;
Q, X, Y' = N or C;
Z' = N or CH;
R1 = -C(O)NR5R6, -N(H)C(O)R7, -C(O)-1-6C alkanediyl SR7, -NR8C(O)N(OH)R7, -NR8C(O)-1-6C alkanediyl SR7, -NR8C(O)C=N(OH)R7 or another Zn-chelating-group;
R5, R6 = H, OH, 1-6C alkyl, hydroxy-1-6C alkyl, amino-1-6C alkyl or aminoaryl;
R7 = H, 1-6C alkyl, 1-6C alkylcarbonyl, aryl-1-6C alkyl, 1-6C alkylpyrazinyl, pyridinone, pyrrolidinone or methylimidazolyl;
R8 = H or 1-6C alkyl;
R2 = H, halo, hydroxy, amino, nitro, 1-6C alkyl, 1-6C alkyloxy, trifluoromethyl, di(1-6C alkyl)amino, hydroxyamino or naphthalenylsulfonylpyrazinyl;
R3 = H, 1-6C alkyl, aryl-2-6C alkenediyl, furanylcarbonyl, naphthalenylcarbonyl, -C(O)phenyl R9, 1-6C alkylaminocarbonyl, aminosulfonyl, arylaminosulfonyl, aminosulfonylamino, di(1-6C alkyl)aminosulfonylamino, arylaminosulfonylamino, aminosulfonylamino-1-6C alkyl, di (1-6C alkyl)aminosulfonylamino-1-6C alkyl, arylaminosulfonylamino-1-6C alkyl, di(1-6C alkyl)amino-1-6C alkyl, 1-12C alkylsulfonyl, di(1-6C alkyl)aminosulfonyl, trihalo-1-6C alkylsulfonyl, di(aryl)-1-6C alkylcarbonyl, thiophenyl-1-6C alkylcarbonyl,

pyridinylcarbonyl or aryl-1-6C alkylcarbonyl;
R9 = phenyl (optionally mono- - tri-substituted by halo, amino, 1-6C alkyl, 1-6C alkyloxy, hydroxy-1-4C alkyl, hydroxy-1-4C alkyloxy, amino-1-4C alkyloxy, di(1-4C alkyl)amino-1-4C alkyloxy, di(1-6C alkyl)amino-1-6C alkyl, di(1-6C alkyl)amino-1-6C alkyl(1-6C alkyl)amino-1-6C alkyl, hydroxy-1-4C alkylpiperazinyl-1-4C alkyl, 1-4C alkyloxypiperidinyl-1-4C alkyl, hydroxy-1-4C alkyloxy-1-4C alkylpiperazinyl, 1-4C alkylpiperazinyl-1-4C alkyl, di(hydroxy-1-4C alkyl)amino-1-4C alkyl, pyrrolidinyl-1-4C alkyloxy, morpholinyl-1-4C alkyloxy or morpholinyl-1-4C alkyl) or thiophenyl (optionally substituted by di(1-4C alkyl)amino-1-4C alkyloxy, di(1-6C alkyl)amino-1-6C alkyl, di(1-6C alkyl)amino-1-6C alkyl(1-6C alkyl)amino-1-6C alkyl, pyrrolidinyl-1-4C alkyloxy, 1-4C alkylpiperazinyl-1-4C alkyl, di(hydroxy-1-4C alkyl)amino-1-4C alkyl or morpholinyl-1-4C alkyloxy);
R4 = H, OH, amino, hydroxy-1-6C alkyl, 1-6C alkyl, 1-6C alkyloxy, aryl-1-6C alkyl, aminocarbonyl, hydroxycarbonyl, amino-1-6C alkyl, aminocarbonyl-1-6C alkyl, hydroxycarbonyl-1-6C alkyl, hydroxyaminocarbonyl, 1-6C alkyloxycarbonyl, 1-6C alkylamino-1-6C alkyl or di(1-6C alkyl)amino-1-6C alkyl or when R3 and R4 are joined to the same carbon, R3+R4 = a bivalent radical of formula -C(O)-NH-CH2-NR10 or when R3 and R4 are joined to adjacent carbons R3+R4 = =CH-CH=CH-CH= ; and
R10 = H or aryl.

The aryl in the substituted phenyl is at least one selected from halo, 1-6C alkyl, 1-6C alkyloxy, trifluoromethyl, cyano or hydroxycarbonyl.

INDEPENDENT CLAIMS are included for the following:

(1) Preparation of (I);

(2) Use of (I) in the manufacture of a medicament for the treatment of proliferative diseases;

(3) Detection or identification of a **histone deacetylase** (HDAC) in a biological sample involving detecting or measuring the formation of a complex between a labelled compound of (I) and HDAC; and

(4) A combination of an anti-cancer agent and (I).

ACTIVITY - Cytostatic; Antipsoriatic; Antiarthritic; Antirheumatic; Osteopathic; Antigout; Dermatological; Antiinflammatory; Immunosuppressive; Antiarteriosclerotic; Vasotropic; Antiulcer; Antiallergic; Ophthalmological; Antiasthmatic; Antiseborrheic; Antidiabetic; Immunomodulator; Hemostatic; Neuroprotective; Respiratory-Gen.; CNS-Gen.; Gynecological; Cardiant; Anti-HIV; Nephrotropic; Antiparkinsonian; Muscular-Gen.; Gastrointestinal-Gen.; Endocrine-Gen.; Nootropic.

MECHANISM OF ACTION - HDAC (**histone deacetylase**) inhibitor.

Human A2780 ovarian carcinoma cells were cultured in RPMI 1640 medium supplemented with L-glutamine (2 mM), gentamicin (50 mu g/ml) and fetal calf serum (10%). Cells were routinely kept as monolayer cultures at 37 deg. C in a humidified CO2 (5%) atmosphere. Cells were passaged once a week using a trypsin/EDTA solution at a split ratio of 1:40. Cells were seeded in NUNC (RTM) 96-well culture plates and allowed to adhere to the plastic overnight. After cell adhesion to the plates, medium was changed, drugs and/or solvents were added to a final volume of (200 mu l). Following four days of incubation, medium was replaced by fresh medium (200 mu l), cell density and viability was assessed using an MTT-based assay. To each well MTT (25 mu l) solution was added and the cells were further incubated for 2 hours at 37 deg. C. N-Hydroxy-4-(4-(octane-1-sulfonyl)-piperazin-1-yl)-benzamide (A) was tested at a single fixed concentration of 10-6. (A) showed IC50 value of 6.166.

USE - (I) Are useful in the manufacture of a medicament for the treatment of proliferative diseases (claimed). Also used for the sensitization of tumors to radiotherapy use for the treatment of cancer (e.g. lung cancer, pancreatic cancer, colon cancer, prostate cancer, hematopoietic tumors of lymphoid lineage, myeloid leukemias, thyroid

follicular cancer, myelodysplastic syndrome (MDS), tumors of mesenchymal origin, melanomas, teratocarcinomas, neuroblastomas, gliomas, benign tumor of the skin, breast carcinoma, kidney carcinoma, ovary carcinoma, bladder carcinoma and epidermal carcinoma), treating arthropathies and osteopathological conditions e.g. rheumatoid arthritis, osteoarthritis, juvenile arthritis, gout, polyarthritis, psoriatic arthritis, ankylosing spondylitis and systemic lupus erythematosus), inhibiting smooth muscle cell proliferation including vascular proliferative disorders, atherosclerosis and restenosis), treating inflammatory conditions and dermal conditions (e.g. ulcerative colitis, Crohn's disease, allergic rhinitis, graft vs. host disease, conjunctivitis, asthma, adult respiratory distress syndrome (ARDS), Behcet's disease, transplant rejection, uticaria, allergic dermatitis, alopecia areata, scleroderma, exanthema, eczema, dermatomyositis, acne, diabetes, Kawasaki's disease, multiple sclerosis, emphysema, cystic fibrosis and chronic bronchitis), endometriosis, uterine fibroids, dysfunctional uterine bleeding and endometrial hyperplasia, ocular vascularization, cardiac dysfunction, HIV infections, renal dysfunction, neuropathology (e.g. Parkinson's disease, cognitive disorder e.g. Alzheimer's disease and polyglutamine related neuronal diseases), spinal muscular atrophy, pathologic conditions amenable to treatment by potentiating expression of a gene, suppressing endocrine disorders, inhibiting dysfunction of gluconeogenesis, inhibiting a neuromuscular pathology e.g. amylotrophic lateral sclerosis.

ADVANTAGE - The compounds are potent inhibitors of HDAC with high enzymatic activity, show cellular activity increase bioavailability and have little or no side effects.

Dwg.0/0

FS CPI

FA AB; GI; DCN

MC CPI: B06-A02; B06-A03; B06-H; B07-D11; B07-D12; B07-H; B10-A03; B11-C07B; B11-C08; B11-C10; B12-K04E; B14-A02B1; B14-C02; B14-C03; B14-C04; B14-C06; B14-D01; B14-D02; B14-D07A; B14-E10C; B14-F01; B14-F07; B14-F08; B14-G02; B14-H01; B14-H03; B14-J01A3; B14-J01A4; B14-J05; B14-K01; **B14-N03**; B14-N04; B14-N06B; B14-N10; B14-N14; B14-N17; B14-R02; B14-S01; B14-S04

TECH UPTX: 20031117

TECHNOLOGY FOCUS - ORGANIC CHEMISTRY - Preparation (claimed): Preparation of (I) involves reacting an intermediate of formula (II) with an appropriate acid e.g. trifluoro acetic acid to give a hydroxamic acid of formula (III).

ABEX UPTX: 20031117

SPECIFIC COMPOUNDS - 3 Compounds (I) are specifically claimed, i.e. 2-(4-diphenylacetyl-piperazin-1-yl)-pyrimidine-5-carboxylic acid hydroxyamide and 2-(4-(naphthalene-1-carbonyl)-piperazin-1-yl)-pyrimidine-5-carboxylic acid hydroxyamide and N-hydroxy-4-(4-(octane-1-sulfonyl)-piperazin-1-yl)-benzamide (Ia).

ADMINISTRATION - The dosage of (I) is 0.05 - 100 (preferably 0.05 - 10) mg/kg and is administered orally, rectally, percutaneously or parenterally.

EXAMPLE - N-Fmoc-hydroxylamine 2-chlorotrityl resin was deprotected by piperidine (50%) in dimethylformamide (DMF). The resin was washed several times with dichloromethane (DCM), DMF and swelled in DMF. 4-halo benzoic acid (2 equivalent (eq.)), bromo-tris-pyrrolidino-phosphonium hexafluorophosphate and diisopropaylethylamine (DIEA) (4 eq.) were added as one portion. The mixture was shaken for 24 hours, liquid was drained and the resin was washed several times by DCM and DMF. The resin was swelled in DMF containing piperidine (2 eq.), shaken 24 hours at room temperature, the liquid was drained and the resin was washed by DCM and DMF. An octylsulfonyl chloride (2 eq.) was added as one portion to the resin swelled in DMF with triethylamine (4 eq.). Reaction was stirred overnight, drained and the resin was washed by DCM and DMF. The final

product was cleaved by 5% trifluoroacetic acid in DCM, analyzed by HPLC and MS and evaporated in the pre-weighted test-tube to obtain N-hydroxy-4-(4-(octane-1-sulfonyl)-piperazin-1-yl)-benzamide.

DEFINITIONS - Preferred Definitions:
n = 1;
Q = C;
Z' = N;
R1 = -C(O)NH(OH);
R2, R4 = H; and
R3 = naphthalenylcarbonyl, 1-12C alkylsulfonyl or di(aryl)-1-6C alkylcarbonyl.

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AN 2003-779052 [73] WPIX
CR 2003-756805 [71]; 2003-767413 [72]; 2003-779051 [73]; 2003-788172 [74]; 2003-788179 [74]; 2003-853537 [79]; 2003-902761 [82]
DNC C2003-214494
TI New sulfonylamino derivatives, useful as **histone deacetylase** inhibitors for treating proliferative diseases e.g. cancer, psoriasis, rheumatoid arthritis and osteoarthritis.
DC B02 B03
IN ANGIBAUD, P R; BACKX, L J J; DE WINTER, H L J; PILATTE, I N C; VAN BRANDT, S F A; VAN EMELEN, K; VERDONCK, M G C
PA (JANC) JANSSEN PHARM NV
CYC 102
PI WO 2003076401 A1 20030918 (200373)* EN 46 C07D211-58
RW: AT BE BG CH CY CZ DE DK EA EE ES FI FR GB GH GM GR HU IE IT KE LS LU MC MW MZ NL OA PT RO SD SE SI SK SL SZ TR TZ UG ZM ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT RO RU SC SD SE SG SK SL TJ TM TN TR TT TZ UA UG US UZ VC VN YU ZA ZM ZW
AU 2003209727 A1 20030922 (200431) C07D211-58
ADT WO 2003076401 A1 WO 2003-EP2517 20030311; AU 2003209727 A1 AU 2003-209727 20030311
FDT AU 2003209727 A1 Based on WO 2003076401
PRAI **WO 2002-EP14481 20021218; US 2002-363799P 20020313**
IC ICM C07D211-58
ICS A61K031-4545; A61P035-00; C07D207-14; C07D401-04; C07D403-04
AB WO2003076401 A UPAB: 20040514
NOVELTY - Sulfonylamino derivatives (I) and their N-oxide forms, addition salts and isomeric forms are new.
DETAILED DESCRIPTION - Sulfonylamino derivatives of formula (I) and their N-oxide forms, addition salts and isomeric forms are new.
n = 0 - 3;
t = 0 - 4;
Q, X, Y = N or C;
Z = N or CH;
R1 = e.g. NHC(O)R10 or C(O)-1-6C alkanediylSR10;
R10 = e.g. H or alkyl;
R2 = H, halo, OH, amino, nitro, alkyl, alkyloxy, trifluoromethyl, dialkylamino, hydroxyamino or naphthalenylsulfonylpyrazinyl;
R3 = H or one H can be replaced by aryl;
R4 = H, OH, amino, hydroxyalkyl, alkyl, alkyloxy, arylalkyl, aminocarbonyl, hydroxycarbonyl, aminoalkyl, aminocarbonylalkyl, hydroxycarbonylalkyl, hydroxyaminocarbonyl, alkyloxycarbonyl, alkylaminoalkyl or dialkylaminoalkyl;
R5 = H, alkyl, 3-10C cycloalkyl, hydroxyalkyl, alkyloxyalkyl, dialkylaminoalkyl or aryl;
A = e.g. phenyl (substituted by (R6)s);

s = 0 - 5; and
R6 = e.g. H, halo, OH, amino, nitro, trihaloalkyl or trihaloalkyloxy;
alkyl = 1-6C.

Full definitions are given in the DEFINITIONS (Full definitions) Field. INDEPENDENT CLAIMS are also included for the following:

(1) use of (I) in the manufacture of a medicament for the treatment of proliferative diseases;

(2) preparation of (I);

(3) detecting or identifying an HDAC (**histone deacetylase**) in a biological sample involving detecting or measuring the formation of a complex between a labeled (I) and HDAC; and

(4) a combination of an anticancer agent and (I).

ACTIVITY - Cytostatic; Antipsoriatic; Antiarthritic; Antirheumatic; Osteopathic; Antigout; Dermatological; Antiinflammatory; Immunosuppressive; Antiarteriosclerotic; Vasotropic; Antiulcer; Antiallergic; Ophthalmological; Antiasthmatic; Antiseborrheic; Antidiabetic; Immunomodulator; Neuroprotective; Respiratory-Gen.; Gynecological; Cardiant; Anti-HIV; Nephrotropic; Antiparkinsonian; Nootropic; Endocrine-Gen.

MECHANISM OF ACTION - HADC (H2A, H2B, H3 and H4) inhibitors; Smooth muscle cell proliferation inhibitors; Abnormal cell proliferation inhibitors; Apoptosis inducers; Immunosuppressive condition inhibitors; Glyconeogenesis dysfunction inhibitors; Neuromuscular pathology inhibitors; Tumor growth inhibitors.

HeLa nuclear extracts were incubated at 60 micro g/ml with 2 multiply 10-8 M of radiolabeled peptide substrate (synthetic peptide having 14 - 21 amino acids of histone H4). The substrate was biotinylated at the NH2-terminal part with a 6-aminohexanoic acid spacer and was protected at the COOH-terminal part by an amide group and specifically (3H)acetylated at lysine 16. The substrate, biotin-(6-aminohexanoic)Gly-Ala-((3H)-acetyl-Lys-Arg-His-Arg-Lys-Val-NH2), was added in a buffer containing HEPES (4-(2-hydroxyethyl)-1-piperazine ethane sulfonic acid) (25 mM), sucrose (1M), bovine serum albumin (BSA) (0.1 mg/ml) and Triton X-100 (RTM) (0.01%) at pH 7.4. After 30 minutes, the deacetylation reaction was terminated. The resulting mixture was incubated with 2-(4-((biphenyl-4-sulfonylamino)-methyl)-piperidin-1-yl)-pyrimidine-5-carboxylic acid hydroxyamide (Ia). (Ia) showed pIC50 (the negative log value of the IC50-value) of 8.199.

USE - For treating proliferative diseases (claimed) e.g. cancer and psoriasis. The cancer includes lung cancer, colon cancer etc. Also useful for the treatment of rheumatoid arthritis, osteoarthritis, juvenile arthritis, gout, polyarthritis, psoriatic arthritis, ankylosing spondylitis, systemic lupus erythematosus, atherosclerosis, restenosis, inflammatory and dermal conditions (e.g. ulcerative colitis, Crohn's disease, allergic rhinitis, graft versus host disease, conjunctivitis, asthma, acute respiratory distress syndrome, Behcet's disease, transplant rejection, urticaria, allergic dermatitis, alopecia areata, scleroderma, exanthema, eczema, dermatomyositis, acne, diabetes, Kawasaki's disease, multiple sclerosis, emphysema, cystic fibrosis and chronic bronchitis), endometriosis, uterine fibroids, disfunctional uterine bleeding endometrial hyperplasia, ocular vascularization (including vasculopathy affecting retinal and choroidal vessels), cardiac dysfunction, HIV infections, renal dysfunction, Parkinson's disease, Alzheimer's disease or neuropathology that results in a cognitive disorder, amyotrophic lateral sclerosis, spinal muscular atrophy and other pathologic conditions amenable to treatment by potentiating expression of a gene; for suppressing endocrine disorders; and for enhancing gene therapy. For detecting or identifying an HDAC in a biological sample (e.g. body tissues or body fluids such as cerebrospinal fluid, blood, plasma, serum, urine, sputum and saliva) involving detecting or measuring the formation of a complex between a labeled (I) and HDAC. Labeling agents include radioisotopes, fluorescent substances, enzymes or luminous substances.

ADVANTAGE - (I) show excellent in vitro HADC inhibiting activity, good metabolic stability, high oral bioavailability and little or no side effects. (I) show advantageous properties with regard to cellular activity and specific properties with regard to inhibition of cell cycle progression at both G1 and G2 checkpoints (p21 induction capacity). (I) show valuable diagnostic properties. (I) have low affinity for P450 enzymes, which reduces the risk of adverse drug-drug interaction, also allowing for a wider safety margin.

Dwg.0/0

FS CPI

FA AB; GI; DCN

MC CPI: B04-B04B1; B04-B04D4; B04-B04D5; B04-B04L; B04-L05; B06-H; B07-H; B11-C07B; B12-K04; B14-A02B1; B14-C02; B14-C04; B14-C06; B14-C09; B14-D07; B14-E10C; B14-F01; B14-F01G; B14-F07; B14-F08; B14-G02C; B14-H01; B14-J01; B14-K01; **B14-N03**; B14-N04; B14-N06B; B14-N10; B14-N14; B14-N16; B14-N17; B14-R02; B14-S01; B14-S03; B14-S04

TECH UPTX: 20031112

TECHNOLOGY FOCUS - ORGANIC CHEMISTRY - Preparation (Claimed): (I) are prepared e.g. by reacting an intermediate of formula (II) with an acid such as trifluoroacetic acid to give (I: R1 = C(O)NH(OH)).

ABEX UPTX: 20031112

SPECIFIC COMPOUNDS - 18 Compounds (I) are specifically claimed, e.g. 2-(4-((biphenyl-4-sulfonylamino)-methyl)-piperidin-1-yl)-pyrimidine-5-carboxylic acid hydroxyamide (Ia).

ADMINISTRATION - Dosage is 0.005 - 100 (preferably 0.005 - 10) mg/kg orally, rectally, percutaneously, parenterally or transdermally. Unit dosage of (I) comprises 0.5 - 500 (preferably 10 - 500) mg (I).

EXAMPLE - A mixture of 2-(4-((4'-methanesulfonyl-biphenyl-2-sulfonylamino)-methyl)-piperidin-1-yl)-pyrimidine-5-carboxylic acid (tetrahydro-pyran-2-yloxy)-amide (IIa) was treated with 5% trifluoroacetic acid solution in a mixture of dichloromethane/methanol (1/1, 2 ml) for 7 days. The solvents were evaporated at room temperature under N2 and the residue treated for a second time with a 5% trifluoroacetic acid solution in a mixture of dichloromethane/methanol (1/1, 2 ml). The resulting mixture was shaken for another 7 days. The solvents were evaporated at room temperature under N2, followed by addition of 1,4-dioxane and repeating the concentration procedure. The sample was dried under N2 overnight at 40 degreesC to give 2-(4-((4'-methanesulfonyl-biphenyl-2-sulfonylamino)-methyl)-piperidin-1-yl)-pyrimidine-5-carboxylic acid hydroxyamide (Ib).

DEFINITIONS - Full Definitions:

n = 0 - 3;

t = 0 - 4;

Q, X , Y = N or C;

Z = N or CH;

R1 = C(O)NR8R9, NHC(O)R10, C(O)-1-6C alkanediylSR10, NR11C(O)N(OH)R10, NR11C(O)-1-6C alkanediylSR10, NR11C(O)C=N(OH)R10 or Zn-chelating group;

R8, R9 = H, OH, alkyl, hydroxyalkyl, aminoalkyl or aminoaryl;

R10 = H, alkyl, alkylcarbonyl, aryl(1-6C)aryl, alkylpyrazinyl, pyridinone, pyrrolidinone or methylimidazolyl;

R11 = H or alkyl;

R2 = H, halo, OH, amino, nitro, alkyl, alkyloxy, trifluoromethyl, dialkylamino, hydroxyamino or naphthalenylsulfonylpyrazinyl;

R3 = H or one H can be replaced by aryl;

R4 = H, OH, amino, hydroxyalkyl, alkyl, alkyloxy, arylalkyl, aminocarbonyl, hydroxycarbonyl, aminoalkyl, aminocarbonylalkyl, hydroxycarbonylalkyl, hydroxyaminocarbonyl, alkyloxycarbonyl, alkylaminoalkyl or dialkylaminoalkyl;

R5 = H, alkyl, 3-10C cycloalkyl, hydroxyalkyl, alkyloxyalkyl, dialkylaminoalkyl or aryl;

A = phenyl, cyclohexane, naphthalen-2-yl , naphthalen-1-yl, indan-1-yl or 1,2,3,4-tetrahydro-naphthalen-6-yl (all substituted by (R6)s);

pyridin-2-yl , pyridin-3-yl , pyrimidin-2-yl , piperidin-4-yl , morpholin-4-yl , 1H-pyrrol-2-yl , thiophen-2-yl , thiophen-3-yl , furan-2-yl , isoxazol-4-yl , isoxazol-5-yl , 1H-imidazol-4-yl , 1H-1lambdaasterisk4asterisk-thiazol-4-yl , thiazolidin-4-yl , 1H-(1,2,4)triazol-1-yl-C(CH3)2- , 1,4-phenylene-2,4-dihydro-(1,2,4)triazol-3-on-4-yl , 1,4-phenylene-yl-isoxazole-4-yl , quinoline-8-yl , quinolin-7-yl , quinoline-3-yl , (1,6)naphthyridin-2-yl , 1H-quinolin-2-one-3-yl , 1H-indol-2-yl , 1H-inden-2-yl , 2,3-dihydro-benzofuran-5-yl , benzothiazol-6-yl , benzo(1,3)dioxol-5-yl , 1,3-dihydro-benzoimidazol-2-on-1-yl , imidazo(2,1-b)thiazol-5-yl , 4H-pyridazino(1,2-a)pyridazin-1-on-2-yl , 1H-benzoimidazol-1-yl , imidazo(1,2-a)pyridin-3-yl , 3,4-dihydro-1H-quinolin-2-on-6-yl , quinolin-6-yl , furan-3-yl , quinolin-2-yl , isoquinolin-3-yl, pyrrolidin1-yl , 2,5-dihydro-pyrazolo(3,4-d)pyrimidin-4-on-5-yl , 3H-thieno(3,2-d)pyrimidin- 4-one-3-yl , 3H-quinazolin-4-on-3-yl , 1H-indol-5-yl , dibenzothiophen-4-yl , dibenzofuran-4-yl or piperazin-1-yl (all substituted by (R7)s);

s = 0 - 5;

R6, R7 = H, halo, OH, amino, nitro, trihaloalkyl, trihaloalkyloxy, alkyl (optionally substituted with aryl or 3-10C cycloalkyl), alkyloxy, alkyloxyalkyloxy, alkylcarbonyl, alkyloxycarbonyl, alkylsulfonyl, cyanoalkyl, hydroxyalkyl, hydroxyalkyloxy, hydroxyalkylamino, aminoalkyloxy, dialkylaminocarbonyl, di(hydroxyalkyl)amino, (aryl)alkylamino, dialkylaminoalkyloxy, dialkylamino(alkylamino), dialkylaminoalkylaminoalkyl, arylsulfonyl, arylsulfonylamino, aryloxy, aryloxyalkyl, aryl(2-6C)alkenediyl, dialkylamino, dialkylaminoalkyl, dialkylaminoalkylamino, dialkylaminoalkylaminoalkyl, dialkylaminoalkylalkylamino, dialkylaminoalkylalkylaminoalkyl, aminosulfonylaminoalkylamino, aminosulfonylaminoalkylaminoalkyl, dialkylaminosulfonylaminoalkylamino, dialkylaminosulfonylaminoalkylaminoalkyl, cyano, thiophenyl (optionally substituted with dialkylaminoalkylalkylaminoalkyl, dialkylaminoalkyl, alkylpiperazinylalkyl, hydroxyalkylpiperazinylalkyl, hydroxy(alkyloxy)(alkylpiperazinyl)alkyl, dialkylaminosulfonylpiperazinylalkyl, alkyloxypiperidinyl, alkyloxypiperidinylalkyl, morpholinylalkyl, hydroxyalkylalkylaminoalkyl or di(hydroxyalkylaminoalkyl), furanyl (optionally substituted with hydroxyalkyl), benzofuranyl, imidazolyl, oxazolyl (optionally substituted with aryl or alkyl), alkyltriazolyl, tetrazolyl, pyrrolidinyl, pyrrolyl, piperidinylalkyloxy, morpholinyl, alkylmorpholinyl, morpholinylalkyloxy, morpholinylalkyl, morpholinylalkylamino, morpholinylalkylaminoalkyl, piperazinyl, alkylpiperazinyl, alkylpiperazinyl(alkyloxy), piperazinylalkyl, naphthalenylsulfonylpiperazinyl, naphthalenylsulfonylpiperidinyl, naphthalenylsulfonyl, alkylpiperazinylalkyl, alkylpiperazinylalkylamino, alkylpiperazinyl(alkylamino)alkyl, alkylpiperazinylsulfonyl, aminosulfonylpiperazinyl(alkyloxy), aminosulfonylpiperazinyl, aminosulfonylpiperazinylalkyl, dialkylaminosulfonylpiperazinyl, dialkylaminosulfonylpiperazinylalkyl, hydroxyalkylpiperazinyl, hydroxy(alkyl)piperazinylalkyl, alkyloxypiperidinyl, alkyloxypiperidinylalkyl, piperidinylamino(alkylamino), piperidinylamino(alkylamino)alkyl, alkylpiperidinyl(hydroxyalkylamino(alkylamino), alkylpiperidinyl(hydroxyalkylamino(alkylamino)alkyl, hydroxy(alkyloxy)(alkylpiperazinyl), hydroxy-alkyloxy-alkylpiperazinyl-alkyl, (hydroxy-alkyl)(alkylamino), hydroxyalkylalkylamino-alkyl, hydroxy-alkylamino-alkyl, di(hydroxy-alkyl)amino-alkyl, pyrrolidinylalkyl, pyrrolidinyl(alkyloxy), thiopyrazolyl, pyrazolyl (optionally di-substituted with alkyl or trihaloalkyl), pyridinyl (optionally substituted with alkyloxy, aryloxy or aryl), pyrimidinyl, tetrahydropyrimidinylpiperazinyl, tetrahydropyrimidinylpiperazinylalkyl, quinolinyl, indole or phenyl (optionally mono- to tri-substituted with halo, amino, nitro, alkyl, alkyloxy, hydroxy(alkyl'), trifluoromethyl, trifluoromethyloxy, hydroxy(alkyl'oxy), alkyl'sulfonyl, alkyl'oxy(alkyl'oxy), alkyl'oxycarbonyl, amino(alkyl'oxy),

di(alkyl')amino-alkyl'oxy, di(alkyl')amino, di(alkyl')aminocarbonyl, di(alkyl')amino(alkyl'), di(alkyl')amino-alkyl'amino(alkyl'), di(alkyl')amino(alkyl')amino, di(alkyl')amino-alkyl'amino-alkyl', di(alkyl')amino-alkyl'(alkyl')amino, di(alkyl')amino-alkyl'(alkyl')amino-alkyl', aminosulfonylamino(alkyl')amino, aminosulfonylamino(alkyl')amino-alkyl', di(alkyl')aminosulfonylamino(alkyl')amino, di(alkyl')aminosulfonylamino(alkyl')aminoalkyl, cyano, piperidinyl(alkyl'oxy), pyrrolidinyl(alkyl'oxy), aminosulfonylpiperazinyl, aminosulfonylpiperazinyl(alkyl'), di(alkyl')aminosulfonylpiperazinyl, di(alkyl')aminosulfonylpiperazinyl-alkyl', hydroxy-alkyl'piperazinyl, hydroxy-alkyl'piperazinyl-alkyl', alkyl'oxypiperidinyl, alkyl'oxypiperidinyl-alkyl', hydroxy-alkyl'oxy-alkyl'piperazinyl, hydroxy-alkyl'oxy-alkyl'piperazinyl-alkyl', hydroxy-alkyl'-alkyl'amino, hydroxy-alkyl'-alkyl'amino-alkyl', di(hydroxy-alkyl')amino, dihydroxy(alkyl')amino-alkyl', furanyl (optionally substituted with -CH=CH-CH=CH-), pyrrolidinyl(alkyl'), pyrrolidinyl(alkyl'oxy), morpholinyl, morpholinyl-alkyl'oxy, morpholinyl-alkyl', morpholinyl-alkyl'amino, morpholinyl-alkyl'amino-alkyl', piperazinyl, alkyl'piperazinyl, alkyl'piperazinyl-alkyl'oxy, piperazinyl-alkyl', alkyl'piperazinyl-alkyl', alkyl'piperazinyl-alkyl'amino, alkyl'piperazinyl-alkyl'amino-alkyl, tetrahydropyrimidinylpiperazinyl, tetrahydropyrimidinylpiperazinyl(alkyl'), piperidinylamino-alkyl'amino, piperidinylamino-alkyl'amino-alkyl', (alkyl'piperidinyl)(hydroxy-alkyl')amino-alkyl'amino, (alkyl'piperidinyl)(hydroxy-alkyl')amino-alkyl'amino-alkyl', pyridinyl-alkyl'oxy, hydroxy-alkyl'amino, hydroxy-alkyl'amino-alkyl', di(alkyl')amino-alkyl'amino, aminothiadiazolyl, aminosulfonylpiperazinyl-alkyl'oxy or thiophenyl-alkyl'amino));
alkyl = 1-6C;
alkyl' = 1-4C;
aryl is phenyl optionally substituted by at least one halo, alkyl, alkyloxy, trifluoromethyl, cyano or hydroxycarbonyl;
R6 and R7 can be placed on the nitrogen in replacement of the hydrogen;
Preferred Definitions:
n = 1 - 2;
t = 0 - 3;
Q = -C=C-;
R1 = C(O)NH(OH);
R2 = H or alkyl;
R4 = H;
R5 = H or alkyloxyalkyl;
A = phenyl (substituted by (R6)s) or naphthalen-2-yl (substituted by (R6)s);
s = 0 or 1;
R6 = H, thiophenyl, furanyl, benzofuranyl or phenyl (optionally substituted with alkyl, alkyloxy, hydroxy(1-4C)alkyl or di(alkyl')amino.

L61 ANSWER 13 OF 28 WPIX COPYRIGHT 2004 THOMSON DERWENT on STN
AN 2003-779051 [73] WPIX
CR 2003-756805 [71]; 2003-767413 [72]; 2003-779052 [73]; 2003-788172 [74]; 2003-788179 [74]; 2003-853537 [79]; 2003-902761 [82]
DNC C2003-214493
TI New piperazinyl-, piperidinyl- or morpholinyl-derivatives, useful for treating e.g. cancer, psoriasis, arthritis, systemic lupus erythematosus, atherosclerosis, restenosis, cystic fibrosis, asthma and multiple sclerosis.
DC B02 B03
IN ANGIBAUD, P R; DYATKIN, A B; MEERPOEL, L; PILATTE, I N C; ROUX, B; TEN HOLTE, P; VAN BRANDT, S F A; VERDONCK, M G C
PA (JANC) JANSSEN PHARM NV
CYC 102
PI WO 2003076400 A1 20030918 (200373)* EN 36 C07D211-58
RW: AT BE BG CH CY CZ DE DK EA EE ES FI FR GB GH GM GR HU IE IT KE LS

LU MC MW MZ NL OA PT RO SD SE SI SK SL SZ TR TZ UG ZM ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK
DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR
KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT
RO RU SC SD SE SG SK SL TJ TM TN TR TT TZ UA UG US UZ VC VN YU ZA
ZM ZW

AU 2003218736 A1 20030922 (200431) C07D211-58

ADT WO 2003076400 A1 WO 2003-EP2514 20030311; AU 2003218736 A1 AU 2003-218736 20030311

FDT AU 2003218736 A1 Based on WO 2003076400

PRAI **US 2002-363799P 20020313**

IC ICM C07D211-58
ICS A61K031-4545; A61P035-00; C07D207-14; C07D401-04; C07D403-04; C12Q001-34

AB WO2003076400 A UPAB: 20040514
NOVELTY - Piperazinyl-, piperidinyl- or morpholinyl-derivatives (I) are new.

DETAILED DESCRIPTION - Piperazinyl-, piperidinyl- or morpholinyl-derivatives of formula (I) or their N-oxide forms, addition salts and isomeric forms.

n = 0-3;

t = 0-4;

Q, X, Y' = N or C;

Z' = N or CH;

R1 = e.g. NHC(O)R9;

R9 = H, 1-6C alkyl, 1-6C alkylcarbonyl, aryl(1-6C)aryl, 1-6C alkylpyrazinyl, pyridinone, pyrrolidinone or methylimidazolyl;

R2 = H, halo, OH, amino, nitro, 1-6C alkyl, 1-6C alkyloxy, trifluoromethyl, di(1-6C alkyl)amino, hydroxyamino or naphthalenesulfonylpyrazinyl;

L' = direct bond, 1-6C alkanediyl, 1-6C alkanediyloxy, amino, carbonyl or aminocarbonyl;

R3 = H;

R4 = e.g. H, OH, amino, hydroxy(1-6C)alkyl, 1-6C alkyloxy, aryl(1-6C)alkyl, aminocarbonyl, hydroxycarbonyl, amino(1-6C)alkyl, aminocarbonyl(1-6C)alkyl, hydroxycarbonyl(1-6C)alkyl, hydroxyaminocarbonyl, 1-6C alkyloxycarbonyl, 1-6C alkylamino(1-6C)alkyl or di(1-6C alkyl)amino(1-6C)alkyl;

A = e.g. phenyl (substituted by (R5)s);

s = 0-5; and

R5 = e.g. H, halo, OH, amino, nitro, trihalo(1-6C)alkyl.

Full definitions are given in the DEFINITIONS (Full definitions and Preferred definitions) section. INDEPENDENT CLAIMS are included for the following:

(1) use of (I) in the manufacture of a medicament for the treatment of proliferative diseases;

(2) preparation of (I);

(3) detecting or identifying a HDAC (**histone deacetylase**) in a biological sample involving detecting or measuring the formation of a complex between a labeled (I) and HDAC; and

(4) a combination of an anticancer agent and (I).

ACTIVITY - Cytostatic; Antipsoriatic; Antiarthritic; Antirheumatic; Osteopathic; Antigout; Dermatological; Antiinflammatory; Immunosuppressive; Antiarteriosclerotic; Vasotropic; Antiulcer; Antiallergic; Ophthalmological; Antiasthmatic; Antiseborrheic; Antidiabetic; Immunomodulator; Hemostatic; Neuroprotective; Respiratory-Gen.; CNS-Gen.; Gynecological; Cardiant; Anti-HIV; Nephrotropic; Antiparkinsonian; Muscular-Gen.; Gastrointestinal-Gen.; Endocrine-Gen.; Nootropic.

MECHANISM OF ACTION - HADC (**Histone deacetylase**) (H2A, H2B, H3 and H4) inhibitors; Apoptosis inducers; Gene therapy.

HeLa nuclear extracts were incubated at 60 mu g/ml with 2 multiply 10-8 M of radiolabeled peptide substrate (synthetic peptide having 14 - 21

amino acids of histone H4). The substrate was biotinylated at the NH2-terminal part with a 6-aminohexanoic acid spacer and was protected at the COOH-terminal part by an amide group and specifically (3H)acetylated at lysine 16. The substrate, biotin-(6-aminohexanoic)Gly-Ala-((3H)-acetyl-Lys-Arg-His-Arg-Lys-Val-NH2), was added in a buffer containing HEPES (4-(2-hydroxyethyl)-1-piperazine ethane sulfonic acid) (25 mM), sucrose (1M), BSA (0.1 mg/ml) and Triton X-100 (RTM) (0.01%) at pH 7.4. After 30 minutes the deacetylation reaction was terminated. The resulting mixture was incubated with 2-(4-naphthalen-2-ylmethyl-piperazin-1-yl)-pyrimidine-5-carboxylic acid hydroxyamide (test compound). The test compound showed pIC50 (the negative log value of the IC50-value) of 8.148.

USE - (I) Are useful as a medicine and in the manufacture of a medicament for the treatment of proliferative diseases (claimed) such as psoriasis and cancer, e.g. lung cancer, colon cancer and leukemia. Also useful for the treatment of rheumatoid arthritis, osteoarthritis, juvenile arthritis, gout, polyarthritis, psoriatic arthritis, ankylosing spondylitis, systemic lupus erythematosus, atherosclerosis, restenosis, inflammatory and dermal conditions (e.g. ulcerative colitis, Crohn's disease, allergic rhinitis, graft versus host disease, conjunctivitis, asthma, acute respiratory distress syndrome, Behcet's disease, transplant rejection, urticaria, allergic dermatitis, alopecia areata, scleroderma, exanthema, eczema, dermatomyositis, acne, diabetes, Kawasaki's disease, multiple sclerosis, emphysema, cystic fibrosis and chronic bronchitis), endometriosis, uterine fibroids, disfunctional uterine bleeding endometrial hyperplasia, ocular vascularization (including vasculopathy affecting retinal and choroidal vessels), cardiac dysfunction, HIV infections, renal dysfunction, Parkinson's disease, Alzheimer's disease or neuropathology that results in a cognitive disorder, amyotrophic lateral sclerosis, spinal muscular atrophy and other pathologic conditions amenable to treatment by potentiating expression of a gene; for suppressing endocrine disorders; and for enhancing gene therapy.

ADVANTAGE - (I) Shows excellent in vitro HADC inhibiting enzymatic activity, good metabolic stability, high oral bioavailability and little or no side effects. (I) shows advantageous properties with regard to cellular activity and specific properties with regard to inhibition of cell cycle progression at both G1 and G2 checkpoints (p21 induction capacity). (I) shows valuable diagnostic properties.

Dwg.0/0

FS CPI

FA AB; GI; DCN

MC CPI: B05-A03B; B06-A03; B06-E05; B06-H; B07-A01; B07-D05; B07-D11; B07-D12; B07-E03; B07-H; B14-A02B1; B14-C02; B14-C03; B14-C04; B14-C06; B14-C09; B14-D01; B14-D02; B14-D07A; B14-E10C; B14-F01; B14-F07; B14-F08; B14-G02; B14-H01; B14-H03; B14-J01A3; B14-J01A4; B14-J05; B14-K01; **B14-N03**; B14-N04; B14-N06B; B14-N10; B14-N14; B14-N17; B14-R02; B14-S01; B14-S04

TECH UPTX: 20031112

TECHNOLOGY FOCUS - ORGANIC CHEMISTRY - Preparation (Claimed): (I) is prepared by reacting an intermediate of formula (II) with an acid such as trifluoroacetic acid to form (I) (in which R1 is C(O)NH(OH)).

ABEX UPTX: 20031112

SPECIFIC COMPOUNDS - 7 Compounds (I) are specifically claimed, e.g. 2-(4-naphthalen-2-ylmethyl-piperazin-1-yl)-pyrimidine-5-carboxylic acid hydroxyamide (Ia).

ADMINISTRATION - (I) Is administered in a dosage of 0.005 - 100 (preferably 0.005 - 10) mg/kg orally, rectally, percutaneously, parenterally or transdermally. A per unit dosage comprises 0.5 - 500 (preferably 10 - 500) mg of (I).

EXAMPLE - A mixture of 2-(4-naphthalen-2-ylmethyl-piperazin-1-yl)-pyrimidine-5-carboxylic acid ethyl ester (0.0008 mmol) and NaOH (0.0016 ml) in ethyl alcohol (10 ml) was stirred and refluxed for 2 hours, then

cooled to room temperature. The resulting mixture was then subjected to basic work up to form 2-(4-naphthalen-2-ylmethyl-piperazin-1-yl)-pyrimidine-5-carboxylic acid hydroxyamide (88% g).
DEFINITIONS - Full Definitions:
n = 0-3;
t = 0-4;
Q, X, Y' = N or C;
Z' = N or CH;
R1 = C(O)NR7R8, NHC(O)R9, C(O)-1-6C alkanediylSR9, NR10C(O)N(OH)R9, NR10C(O)-1-6C alkanediylSR9, NR10C(O)C=N(OH)R9 or Zn-chelating group;
R7, R8 = H, OH, 1-6C alkyl, hydroxy(1-6C)alkyl, amino(1-6C)alkyl or aminoaryl;
R9 = H, 1-6C alkyl, 1-6C alkylcarbonyl, aryl(1-6C)aryl, 1-6C alkylpyrazinyl, pyridinone, pyrrolidinone or methylimidazolyl;
R10 = H or 1-6C alkyl;
R2 = H, halo, OH, amino, nitro, 1-6C alkyl, 1-6C alkyloxy, trifluoromethyl, di(1-6C alkyl)amino, hydroxyamino or naphthalenylsulfonylpyrazinyl;
L' = direct bond, 1-6C alkanediyl, 1-6C alkanediyloxy, amino, carbonyl or aminocarbonyl;
R3 = H;
R4 = H, OH, amino, hydroxy(1-6C)alkyl, 1-6C alkyl, 1-6C alkyloxy, aryl(1-6C)alkyl, aminocarbonyl, hydroxycarbonyl, amino(1-6C)alkyl, aminocarbonyl(1-6C)alkyl, hydroxycarbonyl(1-6C)alkyl, hydroxyaminocarbonyl, 1-6C alkyloxycarbonyl, 1-6C alkylamino(1-6C)alkyl or di(1-6C alkyl)amino(1-6C)alkyl;
A' = phenyl (substituted by (R5)s), cyclohexane (substituted by (R5)s), pyridin-2-yl (substituted by (R6)s), pyridin-3-yl (substituted by (R6)s), pyrimidin-2-yl (substituted by (R6)s), piperidin-4-yl (substituted by (R6)s), morpholin-4-yl (substituted by (R6)s), 1H-pyrrol-2-yl (substituted by (R6)s), thiophen-2-yl (substituted by (R6)s), thiophen-3-yl (substituted by (R6)s), furan-2-yl (substituted by (R6)s), isoxazol-4-yl (substituted by (R6)s), isoxazol-5-yl (substituted by (R6)s), 1H-imidazol-4-yl (substituted by (R6)s), 1H-1lambdaasterisk4asterisk-thiazol-4-yl (substituted by (R6)s), thiazolidin-4-yl (substituted by (R6)s), 1H-(1,2,4)triazol-1-yl-C(CH3)2- (substituted by (R6)s), 1,4-phenylene-2,4-dihydro-(1,2,4)triazol -3-on-4-yl (substituted by (R6)s), 1,4-phenylene-yl-isoxazole-4-yl (substituted by (R6)s), naphthalen-2-yl (substituted by (R6)s), naphthalen-1-yl (substituted by (R6)s), quinoline-8-yl (substituted by (R6)s), quinolin-7-yl (substituted by (R6)s), quinoline-3-yl (substituted by (R6)s), (1,6)naphthyridin-2-yl (substituted by (R6)s), 1H-quinolin-2-one-3-yl (substituted by (R6)s), indan-1-yl (substituted by (R5)s), 1H-indol-2-yl (substituted by (R6)s), 1H-inden-2-yl (substituted by (R6)s), 2,3-dihydro-benzofuran-5-yl (substituted by (R6)s), benzothiazol-6-yl (substituted by (R6)s), benzo(1,3)dioxol-5-yl (substituted by (R6)s), 1,3-dihydro-benzoimidazol-2-on-1-yl (substituted by (R6)s), imidazo(2,1-b)thiazol-5-yl (substituted by (R6)s), 4H-pyridazino(1,2-a)pyridazin-1-on-2-yl (substituted by (R6)s), 1H-benzoimidazol-1-yl (substituted by (R6)s), imidazo(1,2-a)pyridin-3-yl (substituted by (R6)s), 3,4-dihydro-1H-quinolin-2-on-6-yl (substituted by (R6)s), quinolin-6-yl (substituted by (R6)s), furan-3-yl (substituted by (R6)s), quinolin-2-yl (substituted by (R6)s), isoquinolin-3-yl(substituted by (R6)s), 1,2,3,4-tetrahydro-naphthalen-6-yl (substituted by (R5)s), pyrrolidin-1-yl (substituted by (R6)s), 2,5-dihydro-pyrazolo(3,4-d)pyrimidin-4-on-5-yl (substituted by (R6)s), 3H-thieno(3,2-d)pyrimidin-4-one-3-yl (substituted by (R6)s), 3H-quinazolin-4-on-3-yl (substituted by (R6)s), 1H-indol-5-yl (substituted by (R6)s), dibenzothiophen-4-yl (substituted by (R6)s), dibenzofuran-4-yl (substituted by (R6)s) or piperazin-1-yl (substituted by (R6)s);
s = 0-5;
R5, R6 = H, halo, OH, amino, nitro, trihalo(1-6C)alkyl, trihalo(1-6C)alkyloxy, 1-6C alkyl (optionally substituted with aryl or 3-10C cycloalkyl), 1-6C alkyloxy, 1-6C alkyloxy(1-6C)alkyloxy, 1-6C

alkylcarbonyl, 1-6C alkyloxycarbonyl, 1-6C alkylsulfonyl, cyano(1-6C)alkyl, hydroxy(1-6C)alkyl, hydroxy(1-6C)alkyloxy, hydroxy(1-6C)alkylamino, amino(1-6C)alkyloxy, di(1-6C alkyl)aminocarbonyl, di(hydroxy(1-6C)alkyl)amino, (aryl)(1-6C alkyl)amino, di(1-6C alkyl)amino(1-6C)alkyloxy, di(1-6C alkyl)amino(1-6C alkylamino), di(1-6C alkyl)amino(1-6C)alkylamino(1-6C)alkyl, arylsulfonyl, arylsulfonylamino, aryloxy, aryloxy(1-6C)alkyl, aryl(2-6C)alkenediyl, di(1-6C alkyl)amino, di(1-6C alkyl)amino(1-6C alkyl), di(1-6C alkyl)amino(1-6C alkyl)amino, di(1-6C alkyl)amino(1-6C alkyl)amino(1-6C)alkyl, di(1-6C alkyl)amino(1-6C alkyl)(1-6C alkyl)amino, di(1-6C alkyl)amino(1-6C alkyl)(1-6C alkyl)amino(1-6C alkyl), aminosulfonylamino(1-6C alkyl)amino, aminosulfonylamino(1-6C alkyl)amino(1-6C alkyl), di(1-6C alkyl)aminosulfonylamino(1-6C alkyl)amino, di(1-6C alkyl)aminosulfonylamino(1-6C alkyl)amino(1-6C alkyl), cyano, thiophenyl (optionally substituted with di(1-6C alkyl)amino(1-6C alkyl)(1-6C alkyl)amino(1-6C alkyl), di(1-6C alkyl)amino(1-6C alkyl), 1-6C alkylpiperazinyl(1-6C alkyl), hydroxy(1-6C alkyl)piperazinyl(1-6C alkyl), hydroxy(1-6C alkyloxy)(1-6C alkylpiperazinyl)(1-6C alkyl), di(1-6C alkyl)aminosulfonylpiperazinyl(1-6C)alkyl, 1-6C alkyloxypiperidinyl, 1-6C alkyloxypiperidinyl(1-6C alkyl), morpholinyl(1-6C alkyl), hydroxy(1-6C alkyl)(1-6C alkyl)amino(1-6C alkyl) or di(hydroxy(1-6C alkyl)amino(1-6C alkyl)), furanyl (optionally substituted with hydroxy(1-6C alkyl)), benzofuranyl, imidazolyl, oxazolyl (optionally substituted with aryl or 1-6C alkyl), 1-6C alkyltriazolyl, tetrazolyl, pyrrolidinyl, pyrrolyl, piperidinyl(1-6C)alkyloxy, morpholinyl, 1-6C alkylmorpholinyl, morpholinyl(1-6C)alkyloxy, morpholinyl(1-6C alkyl), morpholinyl(1-6C alkyl)amino, morpholinyl(1-6C alkyl)amino(1-6C alkyl), piperazinyl, 1-6C alkylpiperazinyl, 1-6C alkylpiperazinyl(1-6C alkyloxy), piperazinyl(1-6C alkyl), naphthalenylsulfonylpiperazinyl, naphthalenylsulfonylpiperidinyl, naphthalenylsulfonyl, 1-6C alkylpiperazinyl(1-6C alkyl), 1-6C alkylpiperazinyl(1-6C alkyl)amino, 1-6C alkylpiperazinyl(1-6C alkylamino)(1-6C alkyl), 1-6C alkylpiperazinylsulfonyl, aminosulfonylpiperazinyl(1-6C alkyloxy), aminosulfonylpiperazinyl, aminosulfonylpiperazinyl(1-6C alkyl), di(1-6C alkyl)aminosulfonylpiperazinyl, di(1-6C alkyl)aminosulfonylpiperazinyl(1-6C alkyl), hydroxy(1-6C alkyl)piperazinyl, hydroxy(1-6C alkyl)piperazinyl(1-6C alkyl), 1-6C alkyloxypiperidinyl, 1-6C alkyloxypiperidinyl(1-6C alkyl), piperidinylamino(1-6C alkylamino), piperidinylamino(1-6C alkylamino)(1-6C alkyl), 1-6C alkylpiperidinyl(hydroxy(1-6C alkyl)amino(1-6C alkylamino), 1-6C alkylpiperidinyl(hydroxy(1-6C alkyl)amino(1-6C alkylamino)(1-6C alkyl), hydroxy(1-6C alkyloxy)(1-6C alkylpiperazinyl), hydroxy-1-6C alkyloxy-1-6C alkylpiperazinyl-1-6C alkyl, (hydroxy-1-6C alkyl)(1-6C alkylamino), hydroxy(1-6C alkyl)(1-6C alkyl)amino-1-6C alkyl, hydroxy-1-6C alkylamino-1-6C alkyl, di(hydroxy-1-6C alkyl)amino-1-6C alkyl, pyrrolidinyl(1-6C)alkyl, pyrrolidinyl(1-6C alkyloxy), thiopyrazolyl, pyrazolyl (optionally di-substituted with 1-6C alkyl or trihalo(1-6C alkyl)), pyridinyl (optionally substituted with 1-6C alkyloxy, aryloxy or aryl), pyrimidinyl, tetrahydropyrimidinylpiperazinyl, tetrahydropyrimidinylpiperazinyl(1-6C alkyl), quinolinyl, indole or phenyl (optionally mono- - tri-substituted with halo, amino, nitro, 1-6C alkyl, 1-6C alkyloxy, hydroxy(1-4C alkyl), trifluoromethyl, trifluoromethyloxy, hydroxy(1-4C alkyloxy), 1-4C alkylsulfonyl, 1-4C alkyloxy(1-4C alkyloxy), 1-4C alkyloxycarbonyl, amino(1-4C alkyloxy), di(1-4C alkyl)amino-1-4C alkyloxy, di(1-4C alkyl)amino, di(1-4C alkyl)aminocarbonyl, di(1-4C alkyl)amino(1-4C alkyl), di(1-4C alkyl)amino-1-4C alkylamino(1-4C alkyl), di(1-4C alkyl)amino(1-4C alkyl)amino, di(1-4C alkyl)amino-1-4C alkylamino-1-4C alkyl, di(1-4C alkyl)amino-1-4C alkyl(1-4C alkyl)amino, di(1-4C alkyl)amino-1-4C alkyl(1-4C alkyl)amino-1-4C alkyl, aminosulfonylamino(1-4C alkyl)amino, aminosulfonylamino(1-4C alkyl)amino-1-4C alkyl, di(1-4C alkyl)aminosulfonylamino(1-4C alkyl)amino, di(1-4C alkyl)aminosulfonylamino(1-4C alkyl)amino(1-6C alkyl), cyano, piperidinyl(1-4C alkyloxy), pyrrolidinyl(1-4C alkyloxy),

aminosulfonylpiperazinyl, aminosulfonylpiperazinyl(1-4C alkyl), di(1-4C alkyl)aminosulfonylpiperazinyl, di(1-4C alkyl)aminosulfonylpiperazinyl-1-4C alkyl, hydroxy-1-4C alkylpiperazinyl, hydroxy-1-4C alkylpiperazinyl-1-4C alkyl, 1-4C alkyloxypiperidinyl, 1-4C alkyloxypiperidinyl-1-4C alkyl, hydroxy-1-4C alkyloxy-1-4C alkylpiperazinyl, hydroxy-1-4C alkyloxy-1-4C alkylpiperazinyl-1-4C alkyl, hydroxy-1-4C alkyl-1-4C alkylamino, hydroxy-1-4C alkyl-1-4C alkylamino-1-4C alkyl, di(hydroxy-1-4C alkyl)amino, dihydroxy(1-4C alkyl)amino-1-4C alkyl, furanyl (optionally substituted with -CH=CH-CH=CH-), pyrrolidinyl(1-4C alkyl), pyrrolidinyl(1-4C alkyloxy), morpholinyl, morpholinyl-1-4C alkyloxy, morpholinyl-1-4C alkyl, morpholinyl-1-4C alkylamino, morpholinyl-1-4C alkylamino-1-4C alkyl, piperazinyl, 1-4C alkylpiperazinyl, 1-4C alkylpiperazinyl-1-4C alkyloxy, piperazinyl-1-4C alkyl, 1-4C alkylpiperazinyl-1-4C alkyl, 1-4C alkylpiperazinyl-1-4C alkylamino, 1-4C alkylpiperazinyl-1-4C alkylamino-1-6C alkyl, tetrahydropyrimidinylpiperazinyl, tetrahydropyrimidinylpiperazinyl(1-4C alkyl), piperidinylamino-1-4C alkylamino, piperidinylamino-1-4C alkylamino-1-4C alkyl, (1-4C alkylpiperidinyl)(hydroxy-1-4C alkyl)amino-1-4C alkylamino, (1-4C alkylpiperidinyl)(hydroxy-1-4C alkyl)amino-1-4C alkylamino-1-4C alkyl, pyridinyl-1-4C alkyloxy, hydroxy-1-4C alkylamino, hydroxy-1-4C alkylamino-1-4C alkyl, di(1-4C alkyl)amino-1-4C alkylamino, aminothiadiazolyl, aminosulfonylpiperazinyl-1-4C alkyloxy or thiophenyl-1-4C alkylamino)).

Provided that:

(a) when t is 0, then a direct bond is attached to L';

(b) when n is 0, then a direct bond is attached to Z';

(c) R5 and R6 can be placed on the nitrogen in replacement of the hydrogen;

(d) for R3, H-atom can be replaced by aryl; and

(e) aryl is phenyl optionally substituted with at least one halo, 1-6C alkyl, 1-6C alkyloxy, trifluoromethyl, cyano or hydroxycarbonyl.

Preferred Definitions:

n = 1;

t = 0 or 1;

Q = C;

X, Y' = N;

R1 = C(O)NH(OH);

R2 = H;

L' = direct bond;

R3, R4 = H;

A' = piperidin-4-yl (substituted by (R6)s), furan-2-yl (substituted by (R6)s), naphthalen-2-yl (substituted by (R6)s), 3H-quinazolin-4-on-3-yl (substituted by (R6)s) or piperazin-1-yl (substituted by (R6)s);

s = 0, 1 or 4; and

R5, R6 = H, 1-6C alkyl, 1-6C alkyloxy, naphthalenylsulfonyl or phenyl (substituted with hydroxy(1-6C)alkyl or morpholinyl(1-4C)alkyl.

L61 ANSWER 14 OF 28 WPIX COPYRIGHT 2004 THOMSON DERWENT on STN

AN 2003-767413 [72] WPIX

CR 2003-756805 [71]; 2003-779051 [73]; 2003-779052 [73]; 2003-788172 [74]; 2003-788179 [74]; 2003-853537 [79]; 2003-902761 [82]

DNC C2003-210903

TI New heterocyclic amine derivatives are **histone deacetylase** inhibitors, useful for the treatment of proliferative conditions e.g. cancer, psoriasis, arthritis, systemic lupus erythematosus, atherosclerosis and restenosis .

DC B02 B03

IN ANGIBAUD, P R; PONCELET, V S; ROUX, B; VAN EMELEN, K

PA (JANC) JANSSEN PHARM NV

CYC 102

PI WO 2003076430 A1 20030918 (200372)* EN 32 C07D401-12

RW: AT BE BG CH CY CZ DE DK EA EE ES FI FR GB GH GM GR HU IE IT KE LS LU MC MW MZ NL OA PT RO SD SE SI SK SL SZ TR TZ UG ZM ZW

W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT RO RU SC SD SE SG SK SL TJ TM TN TR TT TZ UA UG US UZ VC VN YU ZA ZM ZW

AU 2003212337 A1 20030922 (200431) C07D401-12

ADT WO 2003076430 A1 WO 2003-EP2513 20030311; AU 2003212337 A1 AU 2003-212337 20030311

FDT AU 2003212337 A1 Based on WO 2003076430

PRAI **US 2002-363799P 20020313**

IC ICM C07D401-12
ICS A61K031-506; A61P035-00; C07D403-12; C07D413-12

AB WO2003076430 A UPAB: 20040514

NOVELTY - Heterocyclic amine derivatives (I) are new.

DETAILED DESCRIPTION - Heterocyclic amine derivatives of formula (I) or their N-oxide forms, addition salts and isomeric forms are new.

n, m = 0-3;

t = 0 or 1;

Q, X, Y' = N or -C=C-;

Z = CH2 or O;

R1 = e.g. NHC(O)R7;

R7 = H, 1-6C alkyl, 1-6C alkylcarbonyl, aryl(1-6C)alkyl, 1-6C alkylpyrazinyl, pyridinone, pyrrolidinone or methylimidazolyl;

R2 = H, OH, amino, hydroxy(1-6C)alkyl, 1-6C alkyl, 1-6C alkyloxy, aryl(1-6C)alkyl, aminocarbonyl, hydroxycarbonyl, amino(1-6C)alkyl, aminocarbonyl(1-6C)alkyl, hydroxycarbonyl(1-6C)alkyl, hydroxyaminocarbonyl, 1-6C alkyloxycarbonyl, 1-6C alkylamino(1-6C)alkyl or di(1-6C alkyl)amino(1-6C)alkyl;

L' = 1-6C alkanediyl, carbonyl, sulfonyl or 1-6C alkanediyl substituted with phenyl;

A = phenyl (substituted by (R5)s);

s = 0-5; and

R5 = e.g. H, halo, OH, amino, nitro, trihalo(1-6C)alkyl, trihalo(1-6C)alkyloxy).

Full definitions are given in the DEFINITIONS (Full definitions and Preferred definitions) section. INDEPENDENT CLAIMS are included for the following:

(1) use of (I) in the manufacture of a medicament for the treatment of proliferative diseases;

(2) preparation of (I);

(3) detecting or identifying a HDAC (**histone deacetylase**) in a biological sample involving detecting or measuring the formation of a complex between a labeled (I) and HDAC; and

(4) a combination of an anticancer agent and (I).

ACTIVITY - Cytostatic; Antipsoriatic; Antiarthritic; Antirheumatic; Osteopathic; Antigout; Dermatological; Antiinflammatory; Immunosuppressive; Antiarteriosclerotic; Vasotropic; Antiulcer; Antiallergic; Ophthalmological; Antiasthmatic; Antiseborrheic; Antidiabetic; Immunomodulator; Neuroprotective; Respiratory-Gen.; Gynecological; Cardiant; Anti-HIV; Nephrotropic; Antiparkinsonian; Nootropic; Relaxant; Gastrointestinal-Gen.; Hemostatic; Endocrine-Gen; Muscular-Gen.; CNS-Gen.

MECHANISM OF ACTION - HADC (**histone deacetylase**) (H2A, H2B, H3 and H4) inhibitors; Apoptosis inducers; Gene therapy.

HeLa nuclear extracts were incubated at 60 mu g/ml with 2 multiply 10-8 M of radiolabeled peptide substrate (synthetic peptide having 14 - 21 amino acids of histone H4). The substrate was biotinylated at the NH2-terminal part with a 6-aminohexanoic acid spacer and was protected at the COOH-terminal part by an amide group and specifically (3H)acetylated at lysine 16. The substrate, biotin-(6-aminohexanoic)Gly-Ala-((3H)-acetyl-Lys-Arg-His-Arg-Lys-Val-NH2), was added in a buffer containing Hepes (25 mM), sucrose (1M), BSA (0.1 mg/ml) and Triton X-100 (RTM) (0.01%) at pH 7.4. After 30 minutes the deacetylation reaction was terminated. The

resulting mixture was incubated with N-hydroxy-6-(1-(naphthalene-2-sulfonyl)-piperidin-4-ylamino)-nicotinamide (test compound). The test compound showed pIC50 (the negative log value of the IC50-value) of 7.676.

USE - As a medicine and in the manufacture of a medicament for the treatment of proliferative diseases (claimed) e.g. cancer and psoriasis. The cancer includes lung cancer, colon cancer etc. Also useful for the treatment of rheumatoid arthritis, osteoarthritis, juvenile arthritis, gout, polyarthritis, psoriatic arthritis, ankylosing spondylitis, systemic lupus erythematosus, atherosclerosis, restenosis, inflammatory and dermal conditions (e.g. ulcerative colitis, Crohn's disease, allergic rhinitis, graft versus host disease, conjunctivitis, asthma, acute respiratory distress syndrome, Behcet's disease, transplant rejection, urticaria, allergic dermatitis, alopecia areata, scleroderma, exanthema, eczema, dermatomyositis, acne, diabetes, Kawasaki's disease, multiple sclerosis, emphysema, cystic fibrosis and chronic bronchitis), endometriosis, uterine fibroids, disfunctional uterine bleeding, endometrial hyperplasia, ocular vascularization (including vasculopathy affecting retinal and choroidal vessels), cardiac dysfunction, HIV infections, renal dysfunction, Parkinson's disease, Alzheimer's disease or neuropathology that results in a cognitive disorder, amyotrophic lateral sclerosis, spinal muscular atrophy and other pathologic conditions amenable to treatment by potentiating expression of a gene; for suppressing endocrine disorders; and for enhancing gene therapy.

ADVANTAGE - (I) Shows excellent in vitro HADC inhibiting enzymatic activity, good metabolic stability, high oral bioavailability and little or no side effects. (I) shows advantageous properties with regard to cellular activity and specific properties with regard to inhibition of cell cycle progression at both G1 and G2 checkpoints (p21 induction capacity). (I) shows valuable diagnostic properties.

Dwg.0/0

FS CPI

FA AB; GI; DCN

MC CPI: B06-H; B07-D04B; B07-D05; B07-D06; B07-D12; B07-E03; B07-H; B14-A02B1; B14-C02; B14-C03; B14-C04; B14-C06; B14-C09; B14-D01; B14-D07A; B14-E10C; B14-F01; B14-F07; B14-F08; B14-G02; B14-G02D; B14-H01; B14-J01A3; B14-J01A4; B14-J05C; B14-K01; **B14-N03**; B14-N04; B14-N06B; B14-N10; B14-N14; B14-N17; B14-R02; B14-S01; B14-S03; B14-S04

TECH UPTX: 20031107

TECHNOLOGY FOCUS - ORGANIC CHEMISTRY - Preparation (Claimed): (I) is prepared by reacting an intermediate of formula (II) with an acid such as trifluoroacetic acid to form (I) (in which R1 is C(O)NH(OH)).

ABEX UPTX: 20031107

SPECIFIC COMPOUNDS - 9 Compounds are specifically claimed as (I) e.g. N-hydroxy-6-(1-(naphthalene-2-sulfonyl)-piperidin-4-ylamino)-nicotinamide (Ia).

ADMINISTRATION - (I) Is administered in a dosage of 0.05 - 100 (preferably 0.05 - 10) mg/kg orally, rectally, percutaneously, parenterally or transdermally. A per unit dosage comprises 0.5 - 500 (preferably 10 - 500) mg of (I).

EXAMPLE - Trifluoroacetic acid (0.5 ml) was added to a mixture of 6-(1-(naphthalene-2-sulfonyl)-piperidin-4-ylamino)-N-(tetrahydro-pyran-2-yloxy)-nicotinamide (0.0007 mol) in methyl alcohol (5 ml). The resulting mixture was stirred at room temperature for 18 hours. Additional trifluoroacetic acid (0.5 ml) was added and the mixture was stirred at room temperature for 18 hours. The resulting mixture was then subjected to basic work up to form N-hydroxy-6-(1-(naphthalene-2-sulfonyl)-piperidin-4-ylamino)-nicotinamide (48%).

DEFINITIONS - Full Definitions:

n, m = 0 - 3;

t = 0 or 1;

Q, X, Y' = N or -C=C-;
Z = CH2 or O;
R1 = C(O)NR3R4, NHC(O)R7, C(O)-1-6C alkanediylSR7, NR8C(O)N(OH)R7, NR8C(O)-1-6C alkanediylSR7, NR8C(O)C=N(OH)R7 or Zn-chelating group;
R3 and R4 = H, OH, 1-6C alkyl, hydroxy(1-6C)alkyl, amino(1-6C)alkyl or aminoaryl;
R7 = H, 1-6C alkyl, 1-6C alkylcarbonyl, aryl(1-6C)alkyl, 1-6C alkylpyrazinyl, pyridinone, pyrrolidinone or methylimidazolyl;
R8 = H or 1-6C alkyl;
R2 = H, OH, amino, hydroxy(1-6C)alkyl, 1-6C alkyl, 1-6C alkyloxy, aryl(1-6C)alkyl, aminocarbonyl, hydroxycarbonyl, amino(1-6C)alkyl, aminocarbonyl(1-6C)alkyl, hydroxycarbonyl(1-6C)alkyl, hydroxyaminocarbonyl, 1-6C alkyloxycarbonyl, 1-6C alkylamino(1-6C)alkyl or di(1-6C alkyl)amino(1-6C)alkyl;
L = 1-6C alkanediyl, carbonyl, sulfonyl or 1-6C alkanediyl substituted with phenyl;
A = phenyl (substituted by (R5)s), cyclohexane (substituted by (R5)s), pyridin-2-yl (substituted by (R6)s), pyridin-3-yl (substituted by (R6)s), pyrimidin-2-yl (substituted by (R6)s), piperidin-4-yl (substituted by (R6)s), morpholin-4-yl (substituted by (R6)s), 1H-pyrrol-2-yl (substituted by (R6)s), thiophen-2-yl (substituted by (R6)s), thiophen-3-yl (substituted by (R6)s), furan-2-yl (substituted by (R6)s), isoxazol-4-yl (substituted by (R6)s), isoxazol-5-yl (substituted by (R6)s), 1H-imidazol-4-yl (substituted by (R6)s), 1H-1lambdaasterisk4asterisk-thiazol-4-yl (substituted by (R6)s), thiazolidin-4-yl (substituted by (R6)s), 1H-(1,2,4)trizol-1-yl-C(CH3)2- (substituted by (R6)s), 1,4-phenylene-2,4-dihydro-(1,2,4)triazol -3-on-4-yl (substituted by (R6)s), 1,4-phenylene-yl-isoxazole-4-yl (substituted by (R6)s), naphthalen-2-yl (substituted by (R6)s), naphthalen-1-yl (substituted by (R6)s), quinoline-8-yl (substituted by (R6)s), quinolin-7-yl (substituted by (R6)s), quinoline-3-yl (substituted by (R6)s), (1,6)naphthyridin-2-yl (substituted by (R6)s), 1H-quinolin-2-one-3-yl (substituted by (R6)s), indan-1-yl (substituted by (R5)s), 1H-indol-2-yl (substituted by (R6)s), 1H-inden-2-yl (substituted by (R6)s), 2,3-dihydro-benzofuran-5-yl (substituted by (R6)s), benzothiazol-6-yl (substituted by (R6)s), benzo(1,3)dioxol-5-yl (substituted by (R6)s), 1,3-dihydro-benzoimidazol-2-on-1-yl (substituted by (R6)s), imidazo(2,1-b)thiazol-5-yl (substituted by (R6)s), 4H-pyridazino(1,2-a)pyridazin-1-on-2-yl (substituted by (R6)s), 1H-benzoimidazol-1-yl (substituted by (R6)s), imidazo(1,2-a)pyridin-3-yl (substituted by (R6)s), 3,4-dihydro-1H-quinolin-2-on-6-yl (substituted by (R6)s), quinolin-6-yl (substituted by (R6)s), furan-3-yl (substituted by (R6)s), quinolin-2-yl (substituted by (R6)s), isoquinolin-3-yl(substituted by (R6)s), 1,2,3,4-tetrahydro-naphthalen-6-yl (substituted by (R5)s), pyrrolidin1-yl (substituted by (R6)s), 2,5-dihydro-pyrazolo(3,4-d)pyrimidin-4-on-5-yl (substituted by (R6)s), 3H-thieno(3,2-d)pyrimidin-4-one-3-yl (substituted by (R6)s), 3H-quinazolin-4-on-3-yl (substituted by (R6)s), 1H-indol-5-yl (substituted by (R6)s), dibenzothiophen-4-yl (substituted by (R6)s), dibenzofuran-4-yl (substituted by (R6)s) or piperazin-1-yl (substituted by (R6)s);
s = 0-5; and
R5, R6 = H, halo, OH, amino, nitro, trihalo(1-6C)alkyl, trihalo(1-6C)alkyloxy, 1-6C alkyl (optionally substituted with aryl or 3-10C cycloalkyl), 1-6C alkyloxy, 1-6C alkyloxy(1-6C)alkyloxy, 1-6C alkylcarbonyl, 1-6C alkyloxycarbonyl, 1-6C alkylsulfonyl, cyano(1-6C)alkyl, hydroxy(1-6C)alkyl, hydroxy(1-6C)alkyloxy, hydroxy(1-6C)alkylamino, amino(1-6C)alkyloxy, di(1-6C alkyl)aminocarbonyl, di(hydroxy(1-6C)alkyl)amino, (aryl)(1-6C alkyl)amino, di(1-6C alkyl)amino(1-6C)alkyloxy, di(1-6C alkyl)amino(1-6C alkylamino), di(1-6C alkyl)amino(1-6C)alkylamino(1-6C)alkyl, arylsulfonyl, arylsulfonylamino, aryloxy, aryloxy(1-6C)alkyl, aryl(2-6C)alkenediyl, di(1-6C alkyl)amino, di(1-6C alkyl)amino(1-6C alkyl), di(1-6C alkyl)amino(1-6C alkyl)amino, di(1-6C alkyl)amino(1-6C alkyl)amino(1-6C)alkyl, di(1-6C alkyl)amino(1-6C alkyl)(1-6C alkyl)amino, di(1-6C alkyl)amino(1-6C alkyl)(1-6C

alkyl)amino(1-6C alkyl), aminosulfonylamino(1-6C alkyl)amino, aminosulfonylamino(1-6C alkyl)amino(1-6C alkyl), di(1-6C alkyl)aminosulfonylamino(1-6C alkyl)amino, di(1-6C alkyl)aminosulfonylamino(1-6C alkyl)amino(1-6C alkyl), cyano, thiophenyl (optionally substituted with di(1-6C alkyl)amino(1-6C alkyl)(1-6C alkyl)amino(1-6C alkyl), di(1-6C alkyl)amino(1-6C alkyl), 1-6C alkylpiperazinyl(1-6C alkyl), hydroxy(1-6C alkyl)piperazinyl(1-6C alkyl), hydroxy(1-6C alkyloxy)(1-6C alkylpiperazinyl)(1-6C alkyl), di(1-6C alkyl)aminosulfonylpiperazinyl(1-6C)alkyl, 1-6C alkyloxypiperidinyl, 1-6C alkyloxypiperidinyl(1-6C alkyl), morpholinyl(1-6C alkyl), hydroxy(1-6C alkyl)(1-6C alkyl)amino(1-6C alkyl) or di(hydroxy(1-6C alkyl)amino(1-6C alkyl)), furanyl (optionally substituted with hydroxy(1-6C alkyl)), benzofuranyl, imidazolyl, oxazolyl (optionally substituted with aryl or 1-6C alkyl), 1-6C alkyltriazolyl, tetrazolyl, pyrrolidinyl, pyrrolyl, piperidinyl(1-6C)alkyloxy, morpholinyl, 1-6C alkylmorpholinyl, morpholinyl(1-6C)alkyloxy, morpholinyl(1-6C alkyl), morpholinyl(1-6C alkyl)amino, morpholinyl(1-6C alkyl)amino(1-6C alkyl), piperazinyl, 1-6C alkylpiperazinyl, 1-6C alkylpiperazinyl(1-6C alkyloxy), piperazinyl(1-6C alkyl), naphthalenylsulfonylpiperazinyl, naphthalenylsulfonylpiperidinyl, naphthalenylsulfonyl, 1-6C alkylpiperazinyl(1-6C alkyl), 1-6C alkylpiperazinyl(1-6C alkyl)amino, 1-6C alkylpiperazinyl(1-6C alkylamino)(1-6C alkyl), 1-6C alkylpiperazinylsulfonyl, aminosulfonylpiperazinyl(1-6C alkyloxy), aminosulfonylpiperazinyl, aminosulfonylpiperazinyl(1-6C alkyl), di(1-6C alkyl)aminosulfonylpiperazinyl, di(1-6C alkyl)aminosulfonylpiperazinyl(1-6C alkyl), hydroxy(1-6C alkyl)piperazinyl, hydroxy(1-6C alkyl)piperazinyl(1-6C alkyl), 1-6C alkyloxypiperidinyl, 1-6C alkyloxypiperidinyl(1-6C alkyl), piperidinylamino(1-6C alkylamino), piperidinylamino(1-6C alkylamino)(1-6C alkyl), 1-6C alkylpiperidinyl(hydroxy(1-6C alkyl)amino(1-6C alkylamino), 1-6C alkylpiperidinyl(hydroxy(1-6C alkyl)amino(1-6C alkylamino)(1-6C alkyl), hydroxy(1-6C alkyloxy)(1-6C alkylpiperazinyl), hydroxy-1-6C alkyloxy-1-6C alkylpiperazinyl-1-6C alkyl, (hydroxy-1-6C alkyl)(1-6C alkylamino), hydroxy(1-6C alkyl)(1-6C alkyl)amino-1-6C alkyl, hydroxy-1-6C alkylamino-1-6C alkyl, di(hydroxy-1-6C alkyl)amino-1-6C alkyl, pyrrolidinyl(1-6C)alkyl, pyrrolidinyl(1-6C alkyloxy), thiopyrazolyl, pyrazolyl (optionally di-substituted with 1-6C alkyl or trihalo(1-6C alkyl)), pyridinyl (optionally substituted with 1-6C alkyloxy, aryloxy or aryl), pyrimidinyl, tetrahydropyrimidinylpiperazinyl, tetrahydropyrimidinylpiperazinyl(1-6C alkyl), quinolinyl, indole or phenyl (optionally mono- - tri-substituted with halo, amino, nitro, 1-6C alkyl, 1-6C alkyloxy, hydroxy(1-4C alkyl), trifluoromethyl, trifluoromethyloxy, hydroxy(1-4C alkyloxy), 1-4C alkylsulfonyl, 1-4C alkyloxy(1-4C alkyloxy), 1-4C alkyloxycarbonyl, amino(1-4C alkyloxy), di(1-4C alkyl)amino-1-4C alkyloxy, di(1-4C alkyl)amino, di(1-4C alkyl)aminocarbonyl, di(1-4C alkyl)amino(1-4C alkyl), di(1-4C alkyl)amino-1-4C alkylamino(1-4C alkyl), di(1-4C alkyl)amino(1-4C alkyl)amino, di(1-4C alkyl)amino-1-4C alkylamino-1-4C alkyl, di(1-4C alkyl)amino-1-4C alkyl(1-4C alkyl)amino, di(1-4C alkyl)amino-1-4C alkyl(1-4C alkyl)amino-1-4C alkyl, aminosulfonylamino(1-4C alkyl)amino, aminosulfonylamino(1-4C alkyl)amino-1-4C alkyl, di(1-4C alkyl)aminosulfonylamino(1-4C alkyl)amino, di(1-4C alkyl)aminosulfonylamino(1-4C alkyl)amino(1-6C alkyl), cyano, piperidinyl(1-4C alkyloxy), pyrrolidinyl(1-4C alkyloxy), aminosulfonylpiperazinyl, aminosulfonylpiperazinyl(1-4C alkyl), di(1-4C alkyl)aminosulfonylpiperazinyl, di(1-4C alkyl)aminosulfonylpiperazinyl-1-4C alkyl, hydroxy-1-4C alkylpiperazinyl, hydroxy-1-4C alkylpiperazinyl-1-4C alkyl, 1-4C alkyloxypiperidinyl, 1-4C alkyloxypiperidinyl-1-4C alkyl, hydroxy-1-4C alkyloxy-1-4C alkylpiperazinyl, hydroxy-1-4C alkyloxy-1-4C alkylpiperazinyl-1-4C alkyl, hydroxy-1-4C alkyl-1-4C alkylamino, hydroxy-1-4C alkyl-1-4C alkylamino-1-4C alkyl, di(hydroxy-1-4C alkyl)amino, dihydroxy(1-4C alkyl)amino-1-4C alkyl, furanyl (optionally substituted with -CH=CH-CH=CH-), pyrrolidinyl(1-4C alkyl), pyrrolidinyl(1-4C alkyloxy), morpholinyl, morpholinyl-1-4C alkyloxy,

morpholinyl-1-4C alkyl, morpholinyl-1-4C alkylamino, morpholinyl-1-4C alkylamino-1-4C alkyl, piperazinyl, 1-4C alkylpiperazinyl, 1-4C alkylpiperazinyl-1-4C alkyloxy, piperazinyl-1-4C alkyl, 1-4C alkylpiperazinyl-1-4C alkyl, 1-4C alkylpiperazinyl-1-4C alkylamino, 1-4C alkylpiperazinyl-1-4C alkylamino-1-6C alkyl, tetrahydropyrimidinylpiperazinyl, tetrahydropyrimidinylpiperazinyl(1-4C alkyl), piperidinylamino-1-4C alkylamino, piperidinylamino-1-4C alkylamino-1-4C alkyl, (1-4C alkylpiperidinyl)(hydroxy-1-4C alkyl)amino-1-4C alkylamino, (1-4C alkylpiperidinyl)(hydroxy-1-4C alkyl)amino-1-4C alkylamino-1-4C alkyl, pyridinyl-1-4C alkyloxy, hydroxy-1-4C alkylamino, hydroxy-1-4C alkylamino-1-4C alkyl, di(1-4C alkyl)amino-1-4C alkylamino, aminothiadiazolyl, aminosulfonylpiperazinyl-1-4C alkyloxy or thiophenyl-1-4C alkylamino)).

Provided that:

(a) when n and m is 0, then a direct bond is attached to N;

(b) when t is 0,then a direct bond is attached to NH;

(c) R5 and R6 is replaced on the nitrogen atom in replacement of H; and

(d) aryl is phenyl optionally substituted with at least one halo, 1-6C alkyl, 1-6C alkyloxy, trifluoromethyl, cyano or hydroxycarbonyl.

Preferred Definitions:

t = 0;

n = 0 - 2;

m = 1 - 2;

Q = -C=C-;

X = N;

R1 = C(O)NH(OH);

R2 = H;

L' = carbonyl or sulfonyl;

A = phenyl (substituted by (R5)s) or naphthalen-2-yl (substituted by (R6)s);

s = 0 or 1; and

R5 = H or aryl.

L61 ANSWER 15 OF 28 WPIX COPYRIGHT 2004 THOMSON DERWENT on STN

AN 2003-767390 [72] WPIX

DNC C2003-210880

TI Producing specific mean plasma concentration of **histone deacetylase** inhibitor for selectively inducing terminal differentiation of neoplastic cells involves administering a composition comprising the inhibitor.

DC A96 B05 B07

IN CHIAO, J H; RICHON, V M; BACOPOULOS, N G; MILLER, T A; PARADISE, C M

PA (CHIA-I) CHIAO J H; (RICH-I) RICHON V M; (BACO-I) BACOPOULOS N G; (MILL-I) MILLER T A; (PARA-I) PARADISE C M; (ATON-N) ATON PHARMA INC

CYC 101

PI WO 2003075839 A2 20030918 (200372)* EN 46 A61K000-00

RW: AT BE BG CH CY CZ DE DK EA EE ES FI FR GB GH GM GR HU IE IT KE LS LU MC MW MZ NL OA PT RO SD SE SI SK SL SZ TR TZ UG ZM ZW

W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT RO RU SD SE SG SK SL TJ TM TN TR TT TZ UA UG US UZ VC VN YU ZA ZM ZW

US 2004072735 A1 20040415 (200426) A61K038-12

US 2004087631 A1 20040506 (200430) A61K031-44

AU 2003213684 A1 20030922 (200431) A61K000-00

US 2004122101 A1 20040624 (200442) A61K031-19

US 2004127522 A1 20040701 (200444) A61K031-44

US 2004127523 A1 20040701 (200444) A61K031-44

US 2004132825 A1 20040708 (200445) A61K031-19

ADT WO 2003075839 A2 WO 2003-US6451 20030304; US 2004072735 A1 **Provisional US 2002-361759P 20020304**, US 2003-379149 20030304; US 2004087631 A1 **Provisional US 2002-361759P 20020304**, CIP of US

2003-379149 20030304, US 2003-650025 20030826; AU 2003213684 A1 AU 2003-213684 20030304; US 2004122101 A1 **Provisional US 2002-361759P 20020304**, CIP of US 2003-379149 20030304, US 2003-600132 20030619; US 2004127522 A1 **Provisional US 2002-361759P 20020304**, CIP of US 2003-379149 20030304, US 2003-616649 20030709; US 2004127523 A1 **Provisional US 2002-361759P 20020304**, CIP of US 2003-379149 20030304, US 2003-665079 20030916; US 2004132825 A1 **Provisional US 2002-361759P 20020304**, CIP of US 2003-379149 20030304, US 2003-692523 20031024

FDT AU 2003213684 A1 Based on WO 2003075839

PRAI **US 2002-361759P 20020304**; US 2003-379149 20030304; US 2003-650025 20030826; US 2003-600132 20030619; US 2003-616649 20030709; US 2003-665079 20030916; US 2003-692523 20031024

IC ICM A61K000-00; A61K031-19; A61K031-44; A61K038-12
ICS C07C259-04

AB WO2003075839 A UPAB: 20031107
NOVELTY - Administration of a composition comprising a **histone deacetylase** (HDAC) inhibitor, its salt or hydrate and carrier or diluent produces a mean plasma concentration of at least 10 nM of a HDAC inhibitor in vivo over at least two hours following administration.

DETAILED DESCRIPTION - An INDEPENDENT CLAIM is also included for a composition for oral administration comprising (weight%) HDAC inhibitor (50 - 200, preferably 50 - 70 mg), microcrystalline cellulose (20 - 40), croscarmellose sodium (5 - 15) and magnesium stearate (0.1 - 5).

ACTIVITY - Cytostatic; Antiinflammatory; Antiallergic; Immunosuppressive; Tranquilizer; Antirheumatic; Antiarthritic; Dermatological; Cerebroprotective; Anti-HIV; Cardiant; Hepatotropic; Antithyroid; Respiratory-Gen.; Nootropic; Neuroprotective; Immunomodulator; Antiasthmatic; Antiarteriosclerotic; Muscular-Gen.; Antipyretic; Antidiabetic; Nephrotropic; Hemostatic; Analgesic; Osteopathic; Antiparkinsonian; Tocolytic; Vasotropic; Antibacterial; Anticonvulsant; Neuroleptic; Ophthalmological.

Patient having adult solid tumors were first treated with suberoylanilide hydroxamic acid (SAHA) (200 mg) intravenously over two hours. Starting on second day, patients were treated with daily doses of oral SAHA (200 mg) in a single capsule. Blood samples were taken on day one and day 21 of oral treatment. Serum plasma levels of intravenous/oral (fasting) SAHA was measured and was as follows: maximum concentration of SAHA (Cmax) (ng/ml) = 1329/225; half-life (t2) (minute) = 20/80; and area under curve (mg/ml) minute = 153000/25000.

MECHANISM OF ACTION - **Histone deacetylase** (HDAC) inhibitor.

USE - For selectively inducing terminal differentiation of neoplastic cells thus inhibiting proliferation of such cells, cell growth arrest and apoptosis of neoplastic cells (claimed); for treating tumors, cancer (e.g. lung cancer, acute lymphoid myeloma, Hodgkins lymphoma, non-Hodgkins lymphoma, bladder melanoma, renal carcinoma, breast carcinoma, prostate carcinoma, ovarian carcinoma and colorectal carcinoma), acute and chronic inflammatory diseases, autoimmune diseases, allergic diseases, diseases associated with oxidative stress, and cellular hyperproliferation (e.g. rheumatoid arthritis and psoriatic arthritis; inflammatory bowel diseases such as Crohn's disease and ulcerative colitis; spondyloarthropathies; scleroderma; psoriasis, inflammatory dermatoses such an dermatitis, eczema, atopic dermatitis, allergic contact dermatitis, urticaria; vasculitis; eosinphilic myositis, eosinophilic fasciitis; cancers with leukocyte infiltration of the skin or organs, ischemic injury, including cerebral ischemia; HIV, heart failure, chronic, acute or malignant liver disease, autoimmune thyroiditis; systemic lupus erythematosus, Sjorgren's syndrome, lung diseases (e.g. ARDS); acute pancreatitis; amyotrophic lateral sclerosis (ALS); Alzheimer's disease; cachexia/anorexia; asthma; atherosclerosis; chronic fatigue syndrome, fever; diabetes; glomerulonephritis; graft versus host rejection; hemohorragic shock;

hyperalgesia; multiple sclerosis; myopathies; osteoporosis; Parkinson's disease; pain; preterm labor; reperfusion injury; cytokine-induced toxicity (e.g. septic shock, endotoxic shock); side effects from radiation therapy, temporal mandibular joint disease, tumor metastasis; or an inflammatory condition resulting from strain, sprain, cartilage damage, trauma such as burn, orthopedic surgery, infection or other disease processes; respiratory allergic diseases such as allergic rhinitis, hypersensitivity lung diseases, hypersensitivity pneumonitis, eosinophilic pneumonias, delayed-type hypersentitivity, interstitial lung diseases (ILD) (e.g. idiopathic pulmonary fibrosis); systemic anaphylaxis or hypersensitivity responses, drug allergies, insect sting allergies, neurodegenerative diseases, progressive dementia, neurologic signs; and Pick's disease (lobar atrophy), Huntington's disease, multiple system atrophy combining dementia with ataxia, progressive supranuclear palsy (Steel-Richardson-Olszewski), diffuse Lewy body disease, and corticodentatonigral degeneration); Hallervorden-Spatz disease and progressive familial myoclonic epilepsy; syndromes of gradually developing abnormalities of posture and movement such as paralysis agitans, striatonigral degeneration, torsion dystonia (torsion spasm; dystonia musculorum deformans), spasmodic torticollis and other dyskinesis, familial tremor, and Gilles de la Tourette syndrome; syndromes of progressive ataxia such as cerebellar degenerations (e.g. cerebellar cortical degeneration and olivopontocerebellar atrophy (OPCA)); spinocerebellar degeneration (Friedreich's atazia and related disorders); syndrome of central autonomic nervous system failure (Shy-Drager syndrome); syndromes of muscular weakness and wasting without sensory changes (motorneuron disease such as amyotrophic lateral sclerosis, spinal muscular atrophy (e.g. infantile spinal muscular atrophy (Werdnig-Hoffman), juvenile spinal muscular atrophy (Wohlfart-Kugelberg-Welander) and other forms of familial spinal muscular atrophy), primary lateral sclerosis, and hereditary spastic paraplegia; syndromes combining muscular weakness and wasting with sensory changes (e.g. peroneal muscular atrophy; retinitis pigmentosa; hereditary optic atrophy.

ADVANTAGE - The composition produces a mean plasma concentration of HDAC inhibitor of at least 10 nM in vivo for a period of at least 10 hours or at least 2.5 micro M over at least 2 hours following administration. The composition induces differetiation of tumor cells. The composition provides high, stable and prolonged blood levels of HDAC inhibitor and are easy to administer to patient by any conventional mode of oral administration. The intravenous administration provides heavy burden on the patient but the oral administration of HDAC inhibitor provides high and steady levels of the active compounds in-vivo without the need to continuously administer the compound.

Dwg.0/12

FS CPI

FA AB; DCN

MC CPI: A03-A05; A03-C01; A12-V01; B06-H; B07-H; B10-A18; B12-M11C; B14-A01; B14-A02; B14-C01; B14-C03; B14-C04; B14-C09; B14-E08; B14-E10C; B14-F01; B14-F02; B14-F05; B14-F07; B14-G01; B14-G02; B14-H01; B14-J01; B14-J05; B14-K01; B14-K01A; B14-L06; B14-M01; **B14-N03**; B14-N04; B14-N11; B14-N12; B14-N16; B14-S01; B14-S06

TECH UPTX: 20031107

TECHNOLOGY FOCUS - PHARMACEUTICALS - Preferred Composition: The composition is contained within a gelatin capsule. The carrier or diluent is microcrystalline cellulose. The composition further comprises sodium croscarmellose as a disintegrating agent, magnesium stearate as a lubricant.

TECHNOLOGY FOCUS - ORGANIC CHEMISTRY - Preferred Components: The HDAC inhibitor is of formula N(R3)(R4)-C(O)-(CH2)n-C(O)-R2 (I), R-C(O)-NH-(CH2)n1-C(O)-NHOH (II) or R1-NH-C(O)-C(R'4)(A-R'2)-(CH2)n2-C(O)-NHOH (III).

R3 and R4 = optionally substituted, and optionally branched alkyl,

alkenyl, cycloalkyl, aryl, alkyloxy, aryloxy, arylalkyloxy or pyridine;
R3R4 = piperidine;
R2 = hydroxylamino;
n = 5- 8;
R = optionally substituted phenyl, piperidine, thiazole, 2-pyridine, 3-pyridine;
n1 = 4 - 8;
A = amide;
R1 and R'2 = optionally substituted aryl (e.g. phenyl), arylalkyl (e.g. benzyl), naphthyl, pyridineamino, 9-purine-6-amino, thiazoleamino, aryloxy, arylalkyloxy, pyridyl, quinolinyl or isoquinolinyl;
R'4 = H, halo, phenyl or cycloalkyl; and
n2 = 3 - 10.

ABEX UPTX: 20031107
SPECIFIC COMPOUNDS - Suberoylanilide hydroxamic acid and pyroxamide are specifically claimed as the HDAC inhibitor.

ADMINISTRATION - The HDAC inhibitor is administered at a daily dosage of 25 - 4000 (mg/m2) or 200 or 400 mg. The composition is administered orally once daily, twice daily or thrice daily (claimed).

EXAMPLE - No relevant example given.

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AN 2003-756805 [71] WPIX
CR 2003-767413 [72]; 2003-779051 [73]; 2003-779052 [73]; 2003-788172 [74]; 2003-788179 [74]; 2003-853537 [79]; 2003-902761 [82]
DNC C2003-207741
TI New aminocarbonyl derivatives useful for the treatment of proliferative conditions e.g. cancer, psoriasis, rheumatoid arthritis and osteoarthritis.
DC B02 B03
IN DE WINTER, H L J; DYATKIN, A B; MEERPOEL, L; VAN EMELEN, K; VERDONCK, M G C
PA (JANC) JANSSEN PHARM NV
CYC 102
PI WO 2003076421 A1 20030918 (200371)* EN 29 C07D295-20
RW: AT BE BG CH CY CZ DE DK EA EE ES FI FR GB GH GM GR HU IE IT KE LS LU MC MW MZ NL OA PT SD SE SI SK SL SZ TR TZ UG ZM ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT RO RU SC SD SE SG SK SL TJ TM TN TR TT TZ UA UG US UZ VC VN YU ZA ZM ZW
AU 2003212335 A1 20030922 (200431) C07D295-20
AU 2003218735 A1 20030922 (200431) C07D413-04
ADT WO 2003076421 A1 WO 2003-EP2511 20030311; AU 2003212335 A1 AU 2003-212335 20030311; AU 2003218735 A1 AU 2003-218735 20030311
FDT AU 2003212335 A1 Based on WO 2003076421; AU 2003218735 A1 Based on WO 2003076438
PRAI **US 2002-363799P 20020313; WO 2002-EP14833 20021223**
IC ICM C07D295-20; C07D413-04
ICS A61K031-506; A61P035-00; C07D239-42; C07D401-04; C07D403-04
AB WO2003076421 A UPAB: 20040514
NOVELTY - Aminocarbonyl derivatives (I) are new.
DETAILED DESCRIPTION - Aminocarbonyl derivatives of formula (I) or their N-oxide forms, addition salts and isomeric forms are new.
n = 0 - 3;
Q, X and Y = N or -C=C-;
Z = N or CH;
R1 = e.g. NHC(O)R9;
R9 = H, 1-6C alkyl, 1-6C alkylcarbonyl, aryl(1-6C)aryl, 1-6C

alkylpyrazinyl, pyridinone, pyrrolidinone or methylimidazolyl;
R2 = H, halo, OH, amino, nitro, 1-6C alkyl, 1-6C alkyloxy, trifluoromethyl, di(1-6C alkyl)amino, hydroxyamino or naphthalenylsulfonylpyrazinyl;
R3 = e.g. H, OH, amino, hydroxy(1-6C)alkyl, 1-6C alkyl, 1-6C alkyloxy, aryl(1-6C)alkyl, aminocarbonyl, hydroxycarbonyl, amino(1-6C)alkyl, aminocarbonyl(1-6C)alkyl, hydroxycarbonyl(1-6C)alkyl, hydroxyaminocarbonyl, 1-6C alkyloxycarbonyl, 1-6C alkylamino(1-6C)alkyl or di(1-6C alkyl)amino(1-6C)alkyl;
L = direct bond, NH or 1-6C alkanediyl NH;
R4 = H, 1-6C alkyl, 3-10C cycloalkyl, hydroxy(1-6C)alkyl, 1-6C alkyloxy(1-6C)alkyl, di(1-6C alkyl)amino(1-6C)alkyl or aryl;
A = e.g. phenyl (substituted by (R5)s);
s = 0 - 5;
R5 = e.g. H, halo or OH.
Full definitions are given in the DEFINITIONS (Full definitions and Preferred definitions) section. INDEPENDENT CLAIMS are also included for the following:
(1) use of (I) in the manufacture of a medicament for the treatment of proliferative diseases;
(2) preparation of (I);
(3) detecting or identifying a HDAC (**histone deacetylase**) in a biological sample involving detecting or measuring the formation of a complex between a labeled (I) and HDAC; and
(4) a combination of an anticancer agent and (I).
ACTIVITY - Cytostatic; Antipsoriatic; Antiarthritic; Antirheumatic; Osteopathic; Antigout; Dermatological; Antiinflammatory; Immunosuppressive; Antiarteriosclerotic; Vasotropic; Antiulcer; Antiallergic; Ophthalmological; Antiasthmatic; Antiseborrheic; Antidiabetic; Immunomodulator; Neuroprotective; Respiratory-Gen.; Gynecological; Cardiant; Anti-HIV; Nephrotropic; Antiparkinsonian; Nootropic; Relaxant; Endocrine-Gen.
MECHANISM OF ACTION - HADC (H2A, H2B, H3 and H4) inhibitors; Smooth muscle cell proliferation inhibitors; Abnormal cell proliferation inhibitors; Apoptosis inducers; Immunosuppressive condition inhibitors; Glyconeogenesis dysfunction inhibitors; Neuromuscular pathology inhibitors; Gene therapy; Tumor growth inhibitors.
HeLa nuclear extracts were incubated at 60 micro g/ml with 2 multiply 10-8 M of radiolabeled peptide substrate (synthetic peptide having 14 - 21 amino acids of histone H4). The substrate was biotinylated at the NH2-terminal part with a 6-aminohexanoic acid spacer and was protected at the COOH-terminal part by an amide group and specifically (3H)acetylated at lysine 16. The substrate, biotin-(6-aminohexanoic)Gly-Ala-((3H)-acetyl-Lys-Arg-His-Arg-Lys-Val-NH2), was added in a buffer containing Hepes (25 mM), sucrose (1M), BSA (0.1 mg/ml) and Triton X-100 (RTM) (0.01%) at pH 7.4. After 30 minutes the deacetylation reaction was terminated. The resulting mixture was incubated with 2-(4-(biphenyl-4-ylcarbamoyl)-piperazin-1-yl)-pyrimidine-5-carboxylic acid hydroxyamide (test compound). The test compound showed pIC50 (the negative log value of the IC50-value) of 7.728.
USE - As a medicine and in the manufacture of a medicament for the treatment of proliferative diseases (claimed) e.g. cancer and psoriasis. The cancer includes lung cancer, colon cancer etc. Also useful for the treatment of rheumatoid arthritis, osteoarthritis, juvenile arthritis, gout, polyarthritis, psoriatic arthritis, ankylosing spondylitis, systemic lupus erythematosus, atherosclerosis, restenosis, inflammatory and dermal conditions (e.g. ulcerative colitis, Crohn's disease, allergic rhinitis, graft versus host disease, conjunctivitis, asthma, acute respiratory distress syndrome, Behcet's disease, transplant rejection, urticaria, allergic dermatitis, alopecia areata, scleroderma, exanthema, eczema, dermatomyositis, acne, diabetes, Kawasaki's disease, multiple sclerosis, emphysema, cystic fibrosis and chronic bronchitis), endometriosis, uterine fibroids, disfunctional uterine bleeding endometrial hyperplasia, ocular

vascularization (including vasculopathy affecting retinal and choroidal vessels), cardiac dysfunction, HIV infections, renal dysfunction, Parkinson's disease, Alzheimer's disease or neuropathology that results in a cognitive disorder, amyotrophic lateral sclerosis, spinal muscular atrophy and other pathologic conditions amenable to treatment by potentiating expression of a gene; for suppressing endocrine disorders; and for enhancing gene therapy.

ADVANTAGE - (I) shows excellent in vitro HADC inhibiting enzymatic activity, good metabolic stability, high oral bioavailability and little or no side effects. (I) shows advantageous properties with regard to cellular activity and specific properties with regard to inhibition of cell cycle progression at both G1 and G2 checkpoints (p21 induction capacity). (I) shows valuable diagnostic properties.

Dwg.0/0

FS CPI

FA AB; GI; DCN

MC CPI: B06-H; B07-D04B; B07-D05; B07-D10; B07-D11; B07-D12; B07-D13; B07-H; B14-A02B1; B14-C02; B14-C03; B14-C04; B14-C06; B14-C09; B14-D01; B14-E10C; B14-F01; B14-F01G; B14-F07; B14-G02; B14-G02C; B14-H01B; B14-J01A3; B14-J01A4; B14-K01A; B14-K01F; **B14-N03**; B14-N04; B14-N06B; B14-N10; B14-N14; B14-N16; B14-N17; B14-R02; B14-S01; B14-S03; B14-S04

TECH UPTX: 20031105

TECHNOLOGY FOCUS - ORGANIC CHEMISTRY - Preparation (Claimed): (I) is prepared by reacting an intermediate of formula (II) with an acid such as trifluoroacetic acid to form (I) (in which R1 is C(O)NH(OH)).

ABEX UPTX: 20031105

SPECIFIC COMPOUNDS - 4 Compounds are specifically claimed as (I) e.g. 2-(4-(biphenyl-4-ylcarbamoyl)-piperazin-1-yl)-pyrimidine-5-carboxylic acid hydroxyamide (IA).

ADMINISTRATION - (I) is administered in a dosage of 0.05 - 100 (preferably 0.05 - 10) mg/kg orally, rectally, percutaneously, parenterally or transdermally. A per unit dosage comprises 0.5 - 500 (preferably 10 - 500) mg of (I).

EXAMPLE - A mixture of 2-(4-(biphenyl-4-ylcarbamoyl)-piperazin-1-yl)-pyrimidine-5-carboxylic acid ethyl ester (0.0032 mol) and NaOH (0.0128 ml) in ethyl alcohol (20 ml) was stirred at 80 degrees C for 24 hours, then cooled to room temperature. The resulting mixture was then subjected to basic work up to form 2-(4-(biphenyl-4-ylcarbamoyl)-piperazin-1-yl)-pyrimidine-5-carboxylic acid hydroxyamide (75%).

DEFINITIONS - Full Definitions:

n = 0 - 3;

Q, X and Y = N or -C=C-;

Z = N or CH;

R1 = C(O)NR7R8, NHC(O)R9, C(O)-1-6C alkanediylSR9, NR10C(O)N(OH)R9, NR10C(O)-1-6C alkanediylSR9, NR10C(O)C=N(OH)R9 or Zn-chelating group;

R7 and R8 = H, OH, 1-6C alkyl, hydroxy(1-6C)alkyl, amino(1-6C)alkyl or aminoaryl;

R9 = H, 1-6C alkyl, 1-6C alkylcarbonyl, aryl(1-6C)aryl, 1-6C alkylpyrazinyl, pyridinone, pyrrolidinone or methylimidazolyl;

R10 = H or 1-6C alkyl;

R2 = H, halo, OH, amino, nitro, 1-6C alkyl, 1-6C alkyloxy, trifluoromethyl, di(1-6C alkyl)amino, hydroxyamino or naphthalenylsulfonylpyrazinyl;

R3 = H, OH, amino, hydroxy(1-6C)alkyl, 1-6C alkyl, 1-6C alkyloxy, aryl(1-6C)alkyl, aminocarbonyl, hydroxycarbonyl, amino(1-6C)alkyl, aminocarbonyl(1-6C)alkyl, hydroxycarbonyl(1-6C)alkyl, hydroxyaminocarbonyl, 1-6C alkyloxycarbonyl, 1-6C alkylamino(1-6C)alkyl or di(1-6C alkyl)amino(1-6C)alkyl;

L = direct bond, NH or 1-6C alkanediyl NH;

R4 = H, 1-6C alkyl, 3-10C cycloalkyl, hydroxy(1-6C)alkyl, 1-6C

alkyloxy(1-6C)alkyl, di(1-6C alkyl)amino(1-6C)alkyl or aryl;
A = phenyl (substituted by (R5)s), cyclohexane (substituted by (R5)s), pyridin-2-yl (substituted by (R6)s), pyridin-3-yl (substituted by (R6)s), pyrimidin-2-yl (substituted by (R6)s), piperidin-4-yl (substituted by (R6)s), morpholin-4-yl (substituted by (R6)s), 1H-pyrrol-2-yl (substituted by (R6)s), thiophen-2-yl (substituted by (R6)s), thiophen-3-yl (substituted by (R6)s), furan-2-yl (substituted by (R6)s), isoxazol-4-yl (substituted by (R6)s), isoxazol-5-yl (substituted by (R6)s), 1H-imidazol-4-yl (substituted by (R6)s), 1H-1 lambda 4-thiazol-4-yl (substituted by (R6)s), thiazolidin-4-yl (substituted by (R6)s), 1H-(1,2,4)triazol-1-yl-C(CH3)2- (substituted by (R6)s), 1,4-phenylene-2,4-dihydro-(1,2,4)triazol -3-on-4-yl (substituted by (R6)s), 1,4-phenylene-yl-isoxazole-4-yl (substituted by (R6)s), naphthalen-2-yl (substituted by (R6)s), naphthalen-1-yl (substituted by (R6)s), quinoline-8-yl (substituted by (R6)s), quinolin-7-yl (substituted by (R6)s), quinoline-3-yl (substituted by (R6)s), (1,6)naphthyridin-2-yl (substituted by (R6)s), 1H-quinolin-2-one-3-yl (substituted by (R6)s), indan-1-yl (substituted by (R5)s), 1H-indol-2-yl (substituted by (R6)s), 1H-inden-2-yl (substituted by (R6)s), 2,3-dihydro-benzofuran-5-yl (substituted by (R6)s), benzothiazol-6-yl (substituted by (R6)s), benzo(1,3)dioxol-5-yl (substituted by (R6)s), 1,3-dihydro-benzoimidazol-2-on-1-yl (substituted by (R6)s), imidazo(2,1-b)thiazol-5-yl (substituted by (R6)s), 4H-pyridazino(1,2-a)pyridazin-1-on-2-yl (substituted by (R6)s), 1H-benzoimidazol-1-yl (substituted by (R6)s), imidazo(1,2-a)pyridin-3-yl (substituted by (R6)s), 3,4-dihydro-1H-quinolin-2-on-6-yl (substituted by (R6)s), quinolin-6-yl (substituted by (R6)s), furan-3-yl (substituted by (R6)s), quinolin-2-yl (substituted by (R6)s), isoquinolin-3-yl(substituted by (R6)s), 1,2,3,4-tetrahydro-naphthalen-6-yl (substituted by (R5)s), pyrrolidin-1-yl (substituted by (R6)s), 2,5-dihydro-pyrazolo(3,4-d)pyrimidin-4-on-5-yl (substituted by (R6)s), 3H-thieno(3,2-d)pyrimidin-4-one-3-yl (substituted by (R6)s), 3H-quinazolin-4-on-3-yl (substituted by (R6)s), 1H-indol-5-yl (substituted by (R6)s), dibenzothiophen-4-yl (substituted by (R6)s), dibenzofuran-4-yl (substituted by (R6)s) or piperazin-1-yl (substituted by (R6)s);
s = 0 - 5;
R5 and R6 = H, halo, OH, amino, nitro, trihalo(1-6C)alkyl, trihalo(1-6C)alkyloxy, 1-6C alkyl (optionally substituted with aryl or 3-10C cycloalkyl), 1-6C alkyloxy, 1-6C alkyloxy(1-6C)alkyloxy, 1-6C alkylcarbonyl, 1-6C alkyloxycarbonyl, 1-6C alkylsulfonyl, cyano(1-6C)alkyl, hydroxy(1-6C)alkyl, hydroxy(1-6C)alkyloxy, hydroxy(1-6C)alkylamino, amino(1-6C)alkyloxy, di(1-6C alkyl)aminocarbonyl, di(hydroxy(1-6C)alkyl)amino, (aryl)(1-6C alkyl)amino, di(1-6C alkyl)amino(1-6C)alkyloxy, di(1-6C alkyl)amino(1-6C alkylamino), di(1-6C alkyl)amino(1-6C)alkylamino(1-6C)alkyl, arylsulfonyl, arylsulfonylamino, aryloxy, aryloxy(1-6C)alkyl, aryl(2-6C)alkenediyl, di(1-6C alkyl)amino, di(1-6C alkyl)amino(1-6C alkyl), di(1-6C alkyl)amino(1-6C alkyl)amino, di(1-6C alkyl)amino(1-6C alkyl)amino(1-6C)alkyl, di(1-6C alkyl)amino(1-6C alkyl)(1-6C alkyl)amino, di(1-6C alkyl)amino(1-6C alkyl)(1-6C alkyl)amino(1-6C alkyl), aminosulfonylamino(1-6C alkyl)amino, aminosulfonylamino(1-6C alkyl)amino(1-6C alkyl), di(1-6C alkyl)aminosulfonylamino(1-6C alkyl)amino, di(1-6C alkyl)aminosulfonylamino(1-6C alkyl)amino(1-6C alkyl), cyano, thiophenyl (optionally substituted with di(1-6C alkyl)amino(1-6C alkyl)(1-6C alkyl)amino(1-6C alkyl), di(1-6C alkyl)amino(1-6C alkyl), 1-6C alkylpiperazinyl(1-6C alkyl), hydroxy(1-6C alkyl)piperazinyl(1-6C alkyl), hydroxy(1-6C alkyloxy)(1-6C alkylpiperazinyl)(1-6C alkyl), di(1-6C alkyl)aminosulfonylpiperazinyl(1-6C)alkyl, 1-6C alkyloxypiperidinyl, 1-6C alkyloxypiperidinyl(1-6C alkyl), morpholinyl(1-6C alkyl), hydroxy(1-6C alkyl)(1-6C alkyl)amino(1-6C alkyl) or di(hydroxy(1-6C alkyl)amino(1-6C alkyl)), furanyl (optionally substituted with hydroxy(1-6C alkyl)), benzofuranyl, imidazolyl, oxazolyl (optionally substituted with aryl or 1-6C alkyl), 1-6C alkyltriazolyl, tetrazolyl, pyrrolidinyl, pyrrolyl, piperidinyl(1-6C)alkyloxy, morpholinyl, 1-6C alkylmorpholinyl,

morpholinyl(1-6C)alkyloxy, morpholinyl(1-6C alkyl), morpholinyl(1-6C alkyl)amino, morpholinyl(1-6C alkyl)amino(1-6C alkyl), piperazinyl, 1-6C alkylpiperazinyl, 1-6C alkylpiperazinyl(1-6C alkyloxy), piperazinyl(1-6C alkyl), naphthalenylsulfonylpiperazinyl, naphthalenylsulfonylpiperidinyl, naphthalenylsulfonyl, 1-6C alkylpiperazinyl(1-6C alkyl), 1-6C alkylpiperazinyl(1-6C alkyl)amino, 1-6C alkylpiperazinyl(1-6C alkylamino)(1-6C alkyl), 1-6C alkylpiperazinylsulfonyl, aminosulfonylpiperazinyl(1-6C alkyloxy), aminosulfonylpiperazinyl, aminosulfonylpiperazinyl(1-6C alkyl), di(1-6C alkyl)aminosulfonylpiperazinyl, di(1-6C alkyl)aminosulfonylpiperazinyl(1-6C alkyl), hydroxy(1-6C alkyl)piperazinyl, hydroxy(1-6C alkyl)piperazinyl(1-6C alkyl), 1-6C alkyloxypiperidinyl, 1-6C alkyloxypiperidinyl(1-6C alkyl), piperidinylamino(1-6C alkylamino), piperidinylamino(1-6C alkylamino)(1-6C alkyl), 1-6C alkylpiperidinyl(hydroxy(1-6C alkyl)amino(1-6C alkylamino), 1-6C alkylpiperidinyl(hydroxy(1-6C alkyl)amino(1-6C alkylamino)(1-6C alkyl), hydroxy(1-6C alkyloxy)(1-6C alkylpiperazinyl), hydroxy-1-6C alkyloxy-1-6C alkylpiperazinyl-1-6C alkyl, (hydroxy-1-6C alkyl)(1-6C alkylamino), hydroxy(1-6C alkyl)(1-6C alkyl)amino-1-6C alkyl, hydroxy-1-6C alkylamino-1-6C alkyl, di(hydroxy-1-6C alkyl)amino-1-6C alkyl, pyrrolidinyl(1-6C)alkyl, pyrrolidinyl(1-6C alkyloxy), thiopyrazolyl, pyrazolyl (optionally di-substituted with 1-6C alkyl or trihalo(1-6C alkyl)), pyridinyl (optionally substituted with 1-6C alkyloxy, aryloxy or aryl), pyrimidinyl, tetrahydropyrimidinylpiperazinyl, tetrahydropyrimidinylpiperazinyl(1-6C alkyl), quinolinyl, indole or phenyl (optionally mono- - tri-substituted with halo, amino, nitro, 1-6C alkyl, 1-6C alkyloxy, hydroxy(1-4C alkyl), trifluoromethyl, trifluoromethyloxy, hydroxy(1-4C alkyloxy), 1-4C alkylsulfonyl, 1-4C alkyloxy(1-4C alkyloxy), 1-4C alkyloxycarbonyl, amino(1-4C alkyloxy), di(1-4C alkyl)amino-1-4C alkyloxy, di(1-4C alkyl)amino, di(1-4C alkyl)aminocarbonyl, di(1-4C alkyl)amino(1-4C alkyl), di(1-4C alkyl)amino-1-4C alkylamino(1-4C alkyl), di(1-4C alkyl)amino(1-4C alkyl)amino, di(1-4C alkyl)amino-1-4C alkylamino-1-4C alkyl, di(1-4C alkyl)amino-1-4C alkyl(1-4C alkyl)amino, di(1-4C alkyl)amino-1-4C alkyl(1-4C alkyl)amino-1-4C alkyl, aminosulfonylamino(1-4C alkyl)amino, aminosulfonylamino(1-4C alkyl)amino-1-4C alkyl, di(1-4C alkyl)aminosulfonylamino(1-4C alkyl)amino, di(1-4C alkyl)aminosulfonylamino(1-4C alkyl)amino(1-6C alkyl), cyano, piperidinyl(1-4C alkyloxy), pyrrolidinyl(1-4C alkyloxy), aminosulfonylpiperazinyl, aminosulfonylpiperazinyl(1-4C alkyl), di(1-4C alkyl)aminosulfonylpiperazinyl, di(1-4C alkyl)aminosulfonylpiperazinyl-1-4C alkyl, hydroxy-1-4C alkylpiperazinyl, hydroxy-1-4C alkylpiperazinyl-1-4C alkyl, 1-4C alkyloxypiperidinyl, 1-4C alkyloxypiperidinyl-1-4C alkyl, hydroxy-1-4C alkyloxy-1-4C alkylpiperazinyl, hydroxy-1-4C alkyloxy-1-4C alkylpiperazinyl-1-4C alkyl, hydroxy-1-4C alkyl-1-4C alkylamino, hydroxy-1-4C alkyl-1-4C alkylamino-1-4C alkyl, di(hydroxy-1-4C alkyl)amino, dihydroxy(1-4C alkyl)amino-1-4C alkyl, furanyl (optionally substituted with -CH=CH-CH=CH-), pyrrolidinyl(1-4C alkyl), pyrrolidinyl(1-4C alkyloxy), morpholinyl, morpholinyl-1-4C alkyloxy, morpholinyl-1-4C alkyl, morpholinyl-1-4C alkylamino, morpholinyl-1-4C alkylamino-1-4C alkyl, piperazinyl, 1-4C alkylpiperazinyl, 1-4C alkylpiperazinyl-1-4C alkyloxy, piperazinyl-1-4C alkyl, 1-4C alkylpiperazinyl-1-4C alkyl, 1-4C alkylpiperazinyl-1-4C alkylamino, 1-4C alkylpiperazinyl-1-4C alkylamino-1-6C alkyl, tetrahydropyrimidinylpiperazinyl, tetrahydropyrimidinylpiperazinyl(1-4C alkyl), piperidinylamino-1-4C alkylamino, piperidinylamino-1-4C alkylamino-1-4C alkyl, (1-4C alkylpiperidinyl)(hydroxy-1-4C alkyl)amino-1-4C alkylamino, (1-4C alkylpiperidinyl)(hydroxy-1-4C alkyl)amino-1-4C alkylamino-1-4C alkyl, pyridinyl-1-4C alkyloxy, hydroxy-1-4C alkylamino, hydroxy-1-4C alkylamino-1-4C alkyl, di(1-4C alkyl)amino-1-4C alkylamino, aminothiadiazolyl, aminosulfonylpiperazinyl-1-4C alkyloxy or thiophenyl-1-4C alkylamino)).

Provided that:

(a) when n is 0, then a direct bond is attached to Z;

(b) when Z is N, then L is a direct bond; and when Z is CH, then L is NH or 1-6C alkanediyl NH;
(c) R5 and R6 is replaced on the nitrogen atom in replacement of H; and
(d) aryl is phenyl optionally substituted with at least one halo, 1-6C alkyl, 1-6C alkyloxy, trifluoromethyl, cyano or hydroxycarbonyl.
Preferred Definitions:
n = 1;
Q = -C=C-;
X and Y = N;
R1 = C(O)NH(OH);
R2 and R3 = H;
Z = CH;
L = 1-6C alkanediyl NH;
R4 = H, 1-6C alkyl or aryl;
A = phenyl (substituted by (R5)s);
s = 0 or 1;
R5 = H or phenyl.

L61 ANSWER 17 OF 28 WPIX COPYRIGHT 2004 THOMSON DERWENT on STN
AN 2003-731493 [69] WPIX
DNC C2003-201318
TI New recombinant lentiviral gene transfer system, useful for producing replication-defective lentiviral vector particles for treating or preventing a disease, e.g. cancer, a neurologic disease, or ocular neovascularization.
DC B04 C06 D16
IN GOLIGHTLY, D; KALEKO, M; LAMBROU, G; LI, M; LUO, T; MOLINA, R
PA (NOVS) NOVARTIS AG
CYC 102
PI WO 2003066810 A2 20030814 (200369)* EN 121 C12N000-00
RW: AT BE BG CH CY CZ DE DK EA EE ES FI FR GB GH GM GR HU IE IT KE LS LU MC MW MZ NL OA PT SD SE SI SK SL SZ TR TZ UG ZM ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT RO RU SC SD SE SG SK SL TJ TM TN TR TT TZ UA UG US UZ VC VN YU ZA ZM ZW
AU 2003225544 A1 20030902 (200425) C12N000-00
ADT WO 2003066810 A2 WO 2003-US3307 20030204; AU 2003225544 A1 AU 2003-225544 20030204
FDT AU 2003225544 A1 Based on WO 2003066810
PRAI **US 2002-433956P 20021218; US 2002-353177P 20020204**
IC ICM C12N000-00
AB WO2003066810 A UPAB: 20031027
NOVELTY - A recombinant lentiviral gene transfer system, is new.
DETAILED DESCRIPTION - A recombinant lentiviral gene transfer system comprises:
(a) a packaging construct comprising a DNA segment comprising a promoter operably linked to a bovine immunodeficiency virus (BIV) gag gene and a BIV pol gene, or a first packaging construct comprising a DNA segment comprising a first promoter operably linked to a DNA segment comprising a BIV gag gene and a second packaging construct comprising a DNA segment comprising a second promoter operably linked to a DNA segment comprising a BIV pol gene;
(b) a viral surface protein gene construct comprising a DNA segment comprising a promoter operably linked to a viral surface protein gene;
(c) a transfer vector construct comprising a DNA segment comprising a promoter operably linked to a first R region, a U5 region, an untranslated region (UTR) region, a BIV packaging sequence, a Rev response element (RRE) sequence, a promoter operably linked to a heterologous gene of interest, a 3' polypurine tract region, a U3 region, and a second R region; and

(d) a rev gene located on one of the packaging, viral surface protein gene, and transfer vector constructs, or a rev construct comprising a DNA segment comprising a promoter operably linked to a rev gene.

INDEPENDENT CLAIMS are included for the following:

(1) a producer cell comprising the gene transfer system cited above;

(2) producing replication-defective lentiviral vector particles comprising growing the producer cell of (1) in cell culture media under cell culture conditions that allow production of replication-defective lentiviral vector particles by the cell, and collecting the replication-defective lentiviral vector particles from the media;

(3) a replication-defective lentiviral vector particle (I) produced by the method of (2);

(4) treating or preventing a disease in an animal which has or is at risk of contracting the disease, comprising infecting one or more cells of the animal with (I), where the heterologous gene of interest encodes a therapeutic product that is effective in treating or preventing the disease;

(5) transducing cells in vitro or in vivo with a recombinant lentiviral vector particle, comprising contacting the cells with (I);

(6) expressing a heterologous gene of interest in a cell, comprising transducing the cell with (I);

(7) a packaging cell comprising:

(a) a packaging construct comprising a DNA segment comprising a promoter operably linked to a BIV gag gene and a BIV pol gene, or a first packaging construct comprising a DNA segment comprising a first promoter operably linked to a DNA segment comprising a BIV gag gene and a second packaging construct comprising a DNA segment comprising a second promoter operably linked to a DNA segment comprising a BIV pol gene;

(b) a viral surface protein gene construct comprising a DNA segment comprising a promoter operably linked to a viral surface protein gene; and

(c) a rev gene located on one of the packaging, viral surface protein gene, and transfer vector constructs, or a rev construct comprising a DNA segment comprising a promoter operably linked to a rev gene;

(8) an isolated BIV POL protein comprising an amino acid sequence at least 90% identical to a fully defined sequence of 1035 amino acids (P1) given in the specification; and

(9) an isolated nucleic acid molecule comprising:

(a) a nucleotide sequence encoding the BIV POL protein, where the nucleotide sequence consists essentially of a fully defined sequence of 3108 or 3111 bp given in the specification;

(b) a minimal BIV packaging sequence, which is at least 90% identical to a fully defined sequence of 210 bp (N1) given in the specification;

(c) a nucleotide sequence encoding a BIV REV protein, where the nucleotide sequence encodes an amino acid sequence at least 90% identical to the amino acid sequence encoded by a fully defined sequence of 561 bp (N2) given in the specification; or

(d) a minimal BIV RRE sequence, which is at least 90% identical to a fully defined sequence of 312 bp (N3) given in the specification.

ACTIVITY - Ophthalmological; Antidiabetic; Antiulcer; Antiinflammatory; Cytostatic; Immunosuppressive; Neuroprotective; Vasotropic.

A bovine immunodeficiency virus (BIV) vector encoding murine endostatin, and anti-angiogenesis gene, was administered via subretinal injection of transgenic mice that express vascular endothelial growth factor (VEGF) from mouse photoreceptor cells upon induction with doxycycline. BIV vectors were injected into the right eyes of the mice while the left eyes served as control without injection of vectors. Three weeks after vector injection, 0.5 mg/ml of doxycycline was placed in the drinking water for the transgenic mice. Doxycycline induced VEGF expression resulting in severe neovascularization on the left eyes of the transgenic mice. The VEGF-induced neovascularization was completely blocked by BIV vector-mediated endostatin expression in the right eyes in the same animals.

MECHANISM OF ACTION - Gene Therapy.

USE - The recombinant lentiviral gene transfer system is useful for producing replication-defective lentiviral vector particles. The replication-defective lentiviral vector particles are useful in treating or preventing a disease in an animal which has or is at risk of contracting the disease, e.g. ocular neovascularization, wet age related macular degeneration (AMD), diabetic proliferative retinopathy, non-diabetic retinopathy, diabetic macular edema, branch vein occlusion, central retinal vein occlusion, retinopathy in premature infants, rubeosis iridis, neovascular glaucoma, perifoveal telangiectasis, sickle cell retinopathy, Eale's disease, retinal vasculitis, Von Hippel Lindau disease, radiation retinopathy, retinal cryoinjury, retinitis pigmentosa, retinochoroidal coloboma, corneal neovascularization due to herpes simplex, keratitis, corneal ulcers, keratoplasty, pterigyia, or trauma-retinal dystrophy, pathological aging, retinitis pigmentosa, Bardet-Biedel syndrome, Bass en-kornzweig syndrome, Best disease, choroidema, gyrate atrophy, congenital amourosis, Refsun syndrome, Stargardt disease, Usher syndrome, cancer, graft-versus-host disease associated with allogeneic bone marrow transplant, or a neurologic disease (all claimed). The gene transfer system can be used to provide a method of nucleic acid transfer to a dividing or non-dividing cell to provide expression of a particular nucleic acid sequence.

Dwg.0/8

FS CPI

FA AB; DCN

MC CPI: B04-E02E; B04-E02F; B04-E04; B04-E08; B04-F0200E; B04-F1100E; B04-L0100E; B04-N03A0E; B14-C03; B14-E08; B14-F02; **B14-N03**; B14-S03; B14-S04; C04-E02E; C04-E02F; C04-E04; C04-E08; C04-F0200E; C04-F1100E; C04-L0100E; C04-N03A0E; C14-C03; C14-E08; C14-F02; **C14-N03**; C14-S03; C14-S04; D05-H12A; D05-H12B2; D05-H12D5; D05-H12E; D05-H12F; D05-H14B2; D05-H17A3; D05-H17A6; D05-H17B3; D05-H17B6; D05-H18

TECH UPTX: 20031027

TECHNOLOGY FOCUS - BIOTECHNOLOGY - Preferred Gene Transfer System: The packaging construct or at least one of the packaging constructs further comprises a Rev response element (RRE) sequence. The rev gene and RRE sequence are from bovine immunodeficiency virus (BIV). The gag gene comprises a recoded nucleotide sequence. The gag and/or pol genes each comprise a recoded nucleotide sequence. The pol gene comprises an ATG start codon at the 5' end. The protease region of the pol gene is mutated in the three amino acid motif of the catalytic center of the protease, where the mutated protease is less toxic to host cells when compared to a non-mutated BIV protease. The protease region encodes a threonine to serine mutation at amino acid 26 of the protease polypeptide. The BIV packaging sequence comprises no more than the first 101 base pairs of the BIV gag gene open reading frame sequence. The packaging sequence consists essentially of the nucleotide sequence of N1. The transfer vector construct comprises a DNA segment comprising a promoter operably linked to a first R region, a U5 region, an untranslated region (UTR) region, a BIV packaging sequence, an RRE sequence, a promoter operably linked to a heterologous gene of interest, a 3' polypurine tract region, a U3 region, a second R region, and a second U5 region. The packaging construct further comprises the rev gene. The viral surface protein gene construct comprises an env gene, such as VSV-G env, LCMV env, LCMV-GP(WE-HPI) env, MoMLV env, Gibbon Ape Leukemia Virus (GaLV) env, an env gene from a member of the phabdoviridae, an alphavirus env gene, a paramyxovirus env gene, a flavivirus env gene, a retrovirus env gene, an arenavirus env gene, a parainfluenza virus env gene, a thogoto virus env gene, or a baculovirus env gene. The viral surface protein gene encodes the G-protein of vesicular-stomatitis virus (VSV-G) env. The rev gene does not include the native rev intron. The rev gene comprises the nucleotide sequence of N2. The gene transfer system comprises an EF-1 promoter operably linked to the rev gene. The RRE sequence consists essentially of the nucleic acid

sequence of N3. At least two of the promoters are the same, or all of the promoters are different. At least one of the promoters is a regulatable promoter. The gene transfer system does not contain a central polypurine tract (cPPT).
Alternatively, the transfer vector construct further comprises a cPPT. The cPPT is the cPPT from Human Immunodeficiency Virus, or a BIV cPPT. The cPPT consists essentially of 535 base pairs corresponding to the nucleotides from base pairs 4758-5293 inclusive of a fully defined sequence of 8960 bp given in the specification. The U3 region comprises an enhancer of polyadenylation. The enhancer of polyadenylation consists essentially of the SV40 late polyadenylation enhancer element. The gene transfer system does not encode at least one of the vif, vpw, vpy, tmx, or tat genes of BIV. One or more nucleotides in the U3 region are altered or deleted such that U3 mediated transcription is diminished or abolished. The gene transfer system comprises a woodchuck hepatitis virus regulatory response element operably linked to the heterologous gene of interest. The heterologous gene of interest encodes a polypeptide consisting of T2-TrpRS, an Eph B receptor, an ephrin B ligand, a fibrinogen E fragment, a soluble receptor for VEGF, angiostatin, endostatin, optineurin, trabecular meshwork protein, a Rod-derived Cone Viability Factor (RdCVF), or an anti-apoptotic gene product. Preferably, the heterologous gene of interest encodes an RdCVF polypeptide comprising any one of 4 fully defined sequences of 101-135 amino acids given in the specification.
Preferred Producer Cell: The gene transfer system is stably integrated into the producer cell's genome. The gene transfer system is transiently transfected into the producer cell.
Preferred Methods: Producing replication-defective lentiviral vector particles further comprises adding a **histone deacetylase** inhibitor to the media. The **histone deacetylase** inhibitor is butyric acid.
In treating or preventing a disease in an animal which has or is at risk of contracting the disease, the animal is a human. The cells are ocular cells. The cells are infected in vivo or in vitro.
Preferred Packaging Cell: The packaging cell is a 293 cell, a 293T cell, a COS cell, a HeLa cell, or a Cf2TH cell.
Preferred Protein: The BIV POL protein comprises the amino acid sequence of P1, or a methionine at the N-terminus of the POL protein.
Preferred Nucleic Acid: The minimal BIV packaging sequence consists essentially of the nucleotide sequence of N1. The nucleotide sequence encoding the BIV REV protein encodes the same amino acid sequence encoded by the nucleotide sequence of N2. The nucleotide sequence is at least 90% identical, or consists essentially of the nucleotide sequence of N2. The minimal BIV RRE sequence consists essentially of the nucleotide sequence of N3.
Preparation: The lentiviral gene transfer system is prepared by standard recombinant techniques.

ABEX UPTX: 20031027

EXAMPLE - The packaging construct was created by ligating the necessary constructs of bovine immunodeficiency virus (BIV) into the mammalian expression plasmid, pCI. The major splice donor site and the coding sequence for gag and pol were isolated as a 4485-base pair BspEI-BstUI fragment from the BIV provirus. The fragment was blunt ended by Klenow treatment, and ligated to pCI linearized with EcoRI and also blunt ended by Klenow treatment to create pCIigp. PCR amplification of the BIV provirus with primers RRE65'NotI and RRE63'NotI created the minimal RRE fragment. The plasmid created was named pCIigpRRE, and was used in the four-component system. A contiguous coding sequence for rev, with two exons fused, was created by two different methods, RT-PCR and PCR SOEing. The transfer vector construct pBIVminivec was derived from pBC4MGppt. The plasmid containing the viral surface protein gene construct was created. The final construct created was designated pBIVfinalvec and had the ATG gag mutated. The entire pBIVfinalvec was then subjected to DNA sequencing to confirm the integrity of the construct.

L61 ANSWER 18 OF 28 WPIX COPYRIGHT 2004 THOMSON DERWENT on STN
AN 2003-645987 [61] WPIX
DNC C2003-176703
TI New cyclic tetrapeptide compounds useful for treating diabetes, fibrosis and cirrhosis.
DC B02 C02
IN FUJIMURA, T; HOSAKA, M; INOUE, T; MATSUOKA, H; MORI, H; OSODA, K; SATOH, S; SAWADA, K; TAKAGAKI, S; URANO, Y; YOSHIZAWA, K
PA (FUJI) FUJISAWA PHARM CO LTD
CYC 101
PI WO 2003057722 A2 20030717 (200361)* EN 224 C07K005-12
RW: AT BE BG CH CY CZ DE DK EA EE ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SI SK SL SZ TR TZ UG ZM ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT RO RU SC SD SE SG SK SL TJ TM TN TR TT TZ UA UG US UZ VC VN YU ZA ZM ZW
AU 2002356443 A1 20030724 (200421) C07K005-12
ADT WO 2003057722 A2 **WO 2002-JP13754 20021227**; AU 2002356443 A1 **AU 2002-356443 20021227**
FDT AU 2002356443 A1 Based on WO 2003057722
PRAI **AU 2002-952117 20021010**; **AU 2001-9779 20011228**
IC ICM C07K005-12
ICS A61K038-12; A61K038-122; A61P029-00; A61P029-000; A61P035-00; A61P035-000; A61P037-06; A61P037-066
AB WO2003057722 A UPAB: 20030923
NOVELTY - Cyclic tetrapeptide compounds (I) or their salts are new.
DETAILED DESCRIPTION - Cyclic tetrapeptide compounds of formula (I) or their salts are new.
R1 = H;
R2 = lower alkyl, aryl, optionally substituted ar(lower)alkyl, heterocyclic(lower)alkyl, cyclo(lower)alkyl(lower)alkyl, lower alkylcarbamoyl(lower)alkyl or arylcarbamoyl(lower)alkyl;
R3, R4 = ar(lower)alkyl or heterocyclic(lower)alkyl (both optionally substituted), H, lower alkyl, or cyclo(lower)alkyl(lower)alkyl; or
R3+R4 = lower alkylene or condensed ring; or
NR3, NR4 = a ring;
R5 = lower alkylene or lower alkenylene;
Y = -C(RY1)(RY2)(RY3) or -N(RY1)(RY2)(RY3);
RY1 = H, halo or optionally protected hydroxy;
RY2 = H, halo, lower alkyl or phenyl;
RY3 = H or lower alkyl;
R8 = H or lower alkyl;
n = 1 or 2; and
provided that:
(1) when R3 is methyl, R4 is methyl or ethyl, R5 is pentylene, R8 is H, n is 1, RY1 is optionally substituted hydroxy, RY2 is methyl and RY3 is H, then R2 is other than unsubstituted benzyl; and
(2) only one of NR3 and NR4 can be a ring.
An INDEPENDENT CLAIM is also included for a commercial package comprising a pharmaceutical composition comprising (I) and a written matter associated with it stating that the composition may or should be used for treating or preventing inflammatory disorders, diabetes, diabetic complications, homozygous thalassemia, fibrosis, cirrhosis, acute promyelocytic leukemia, organ transplant rejections, autoimmune diseases, protazoal infections or tumors.
ACTIVITY - Antiinflammatory; Antidiabetic; Respiratory Gen.; Hepatotropic; Antianemic; Immunosuppressive; Protozoacide; Cytostatic; Antirheumatic; Antiarthritic; Dermatological; Thyromimetic; Neuroprotective; Antipsoriatic; Antiseborrheic; Antipruritic;

Endocrine-Gen.; Ophthalmological; Antiallergic; Antiasthmatic; Antiulcer; Vulnerary; Antimigraine; Gastrointestinal-Gen.; Nephrotropic; Antiparkinsonian; Nootropic; Cerebroprotective; Hemostatic; Thrombolytic; Antithyroid; Osteopathic; Antiarteriosclerotic; Antibacterial; Antiinfertility; Anti-HIV; Cardiant; Respiratory-Gen.; Auditory; Hypotensive; CNS-Gen.; Vasotropic; Antimicrobial.

MECHANISM OF ACTION - **Histone Deacetylase** Inhibitor; T-cell Growth Inhibitor.

T-cell growth inhibitory activity of 5-(4-benzyloxy-benzyl)-8-ethyl-11-(7-hydroxy-6-oxo-octyl)-8-methyl-decahydro-3a,6,9,12-tetraaza-cyclopentacyclododecene-4,7,10,13-tetraone (Ia) was tested on Lewis rat splenic cells (1.5 multiply 105). The cells were incubated in microtiter plates at 37 deg. C for 72 hours and evaluated. (Ia) showed an IC50 value of less than 50 nm.

USE - (I) are used for treating or preventing inflammatory disorder, diabetes, diabetic complication, homozygous thalassemia, fibrosis, cirrhosis, acute promyelocytic leukemia (APL), organ transplant rejections, autoimmune diseases, protozoal infection or tumor (claimed), rejection reactions by transplantation of organs or tissues, graft-versus-host reactions, autoimmune diseases (e.g. rheumatoid arthritis, systemic lupus erythematosus, Hashimoto's thyroiditis, multiple sclerosis, myasthenia gravis and type I diabetes), pathogenic microorganism infection (e.g. Aspergillus fumigatus, Fusarium oxysporum and Trichophyton asteroides), inflammatory or hyperproliferative skin disease or cutaneous manifestations of immunologically-mediated disease (e.g. psoriasis, atopic dermatitis, contact dermatitis, eczematoid dermatitis, seborrheic dermatitis, lichen planus, pemphigus, bullous pemphigoid, epidermolysis bullosa, urticaria, angioedema, vasculitides, erythema, dermal eosinophilia, lupus erythematosus, acne and alopecia areata), autoimmune disease of the eye, reversible obstructive airways disease (e.g. asthma and bronchitis), mucosal or vascular inflammation (e.g. gastric ulcer, ischemic or thrombotic vascular injury, ischemic bowel diseases, enteritis, necrotizing enterocolitis, intestinal damages associated with thermal burns, leukotriene B4-mediated disease), intestinal inflammations/allergies (e.g. coeliac diseases, proctitis, eosinophilic gastroenteritis, mastocytosis, Crohn's disease and ulcerative colitis), food-related allergic diseases with symptomatic manifestation remote from the gastrointestinal tract (e.g. migraine, rhinitis or eczema), renal diseases, nervous disease (e.g. multiple myositis, Guillain-Barre syndrome, Meniere's disease, multiple neuritis, solitary neuritis, cerebral infarction, Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis and radiculopathy), cerebral ischemic disease (e.g. head injury, hemorrhage in brain, cerebral thrombosis, cerebral embolism, cardiac arrest, stroke, transient ischemic attack and hypertensive encephalopathy), endocrine disease (e.g. hyperthyroidism and Basedow's disease), hematic disease (e.g. pure red cell aplasia, aplastic anemia, hypoplastic anemia, idiopathic thrombocytopenic purpura, autoimmune hemolytic anemia, agranulocytosis, pernicious anemia, megaloblastic anemia and anerythroplasia), bone disease, respiratory disease, skin disease (e.g. dermatomyositis, leukoderma vulgaris, ichthyosis vulgaris, photosensitivity and cutaneous T-cell lymphoma), circulatory disease (e.g. arteriosclerosis, atherosclerosis, aortitis syndrome, polyarteritis nodosa and myocardosis), collagen disease (e.g. scleroderma, Wegener's granuloma and Sjogren's syndrome), adiposis, eosinophilic fasciitis, periodontal disease, nephrotic syndrome, male pattern alopecia, alopecia senile, muscular dystrophy, pyoderma and Sezary syndrome, chromosome abnormality-associated disease (e.g. Down's syndrome), Addison's disease, active oxygen-mediated disease (e.g. organ injury), ischemic disease, intestinal disease (e.g. endotoxin shock, pseudomembranous colitis and drug- or radiation-induced colitis), pulmonary disease (such as toxicosis caused by pulmonary oxygen or drugs, lung cancer and pulmonary emphysema), ocular disease (e.g. cataract, iron-storage disease, retinitis, pigmentosa, senile plaques, vitreous

scarring and corneal alkali burn), dermatitis, and other disease (e.g. gingivitis, periodontitis, sepsis, pancreatitis and diseases caused by environmental pollution, aging, carcinogen, metastasis of carcinoma and hypobaropathy), diseases caused by histamine release or leukotriene C4 release, restenosis of coronary artery following angioplasty and prevention of postsurgical adhesions, autoimmune disease and inflammatory condition (e.g. primary mucosal edema, autoimmune atrophic gastritis, premature menopause, male sterility, juvenile diabetes mellitus, pemphigus vulgaris, pemphigoid, sympathetic ophthalmitis, idiopathic leukopenia, active chronic hepatitis and polychondritis), human immunodeficiency virus infection, allergic conjunctivitis, hypertrophic cicatrix and keloid due to trauma, burn or surgery and liver diseases.

Dwg.0/3

FS CPI

FA AB; GI; DCN

MC CPI: B04-C01A; B04-N04A; B14-A02B1; B14-A03; B14-A04; B14-C01; B14-C03; B14-C09B; B14-D01; B14-D07; B14-E08; B14-E10C; B14-F01B; B14-F01G; B14-F02; B14-F03; B14-F07; B14-G02; B14-H01; B14-J01; B14-J05C; B14-K01; B14-N01; B14-N02; **B14-N03**; B14-N04; B14-N06B; B14-N10; B14-N11; B14-N12; B14-N13; B14-N17; B14-P02; B14-R02; B14-S01; B14-S04; B14-S06; C04-C01A; C04-N04A; C14-A02B1; C14-A03; C14-A04; C14-C01; C14-C03; C14-C09B; C14-D01; C14-D07; C14-E08; C14-E10C; C14-F01B; C14-F01G; C14-F02; C14-F03; C14-F07; C14-G02; C14-H01; C14-J01; C14-J05C; C14-K01; C14-N01; C14-N02; **C14-N03**; C14-N04; C14-N06B; C14-N10; C14-N11; C14-N12; C14-N13; C14-N17; C14-P02; C14-R02; C14-S01; C14-S04; C14-S06

TECH UPTX: 20030923

TECHNOLOGY FOCUS - ORGANIC CHEMISTRY - Preparation: Preparation of (I) (where R5 is lower alkenylene) involves reacting a tetrapeptide of formula (II) with a phosphorus of formula P(O)(OCH3)2-CH2-C(O)Y (III) in presence of a base (e.g. barium hydroxide octahydrate).

R10 = lower alkylene.

ABEX UPTX: 20030923

SPECIFIC COMPOUNDS - 1 compound (I) is specifically disclosed, i.e. 5-(4-benzyloxy-benzyl)-8-ethyl-11-(7-hydroxy-6-oxo-octyl)-8-methyl-decahydro-3a,6,9,12-tetraaza-cyclopentacyclododecene-4,7,10,13-tetraone (Ia).

ADMINISTRATION - The dosage is 0.01 - 10 mg/kg for intravenous, 0.1 - 10 mg/kg for intramuscular, and 0.5 - 50 mg for oral administration. Also the administration is topical.

EXAMPLE - To a stirred solution of 5-(4-benzyloxy-benzyl)-8-ethyl-11-(7-diphenyl-tert-butylsilyloxy-6-oxo-octyl)-8-methyl-decahydro-3a,6,9,12-tetraaza-cyclopentacyclododecene-4,7,10,13-tetraone (74.7 mg) in tetrahydrofuran (3 ml) was added tetrabutylammonium fluoride (1 M in tetrahydrofuran, 0.1 ml) at ambient temperature and the mixture was stirred for 40 minutes. After work-up, 5-(4-benzyloxy-benzyl)-8-ethyl-11-(7-hydroxy-6-oxo-octyl)-8-methyl-decahydro-3a,6,9,12-tetraaza-cyclopentacyclododecene-4,7,10,13-tetraone (Ia) (51.6 mg) was obtained.

DEFINITIONS - Preferred Definitions:

n = 1;

R8 = H;

Y = -C(RY1)(RY2)(RY3);

RY3 = H;

R2 = phenyl(lower)alkyl (substituted by lower alkoxy, ar(lower)alkyloxy, cyano, OH, or halo);

R3 and R4 = lower alkyl; and

R5 = lower alkylene.

L61 ANSWER 19 OF 28 WPIX COPYRIGHT 2004 THOMSON DERWENT on STN

AN 2003-449180 [42] WPIX

DNC C2003-119202
TI Use of **histone deacetylase** inhibitor for treating inherited neurodegenerative diseases e.g. brain cancer and polyglutamine expression disease.
DC B05
IN MARKS, P A; RICHON, V M; RIFKIND, R A
PA (MARK-I) MARKS P A; (RICH-I) RICHON V M; (RIFK-I) RIFKIND R A; (SLOK) SLOAN KETTERING INST CANCER RES
CYC 102
PI WO 2003032921 A2 20030424 (200342)* EN 44 A61K000-00
RW: AT BE BG CH CY CZ DE DK EA EE ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SK SL SZ TR TZ UG ZM ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT RO RU SD SE SG SI SK SL TJ TM TN TR TT TZ UA UG US UZ VC VN YU ZA ZM ZW
US 2004087657 A1 20040506 (200430) A61K031-19
EP 1443928 A2 20040811 (200452) EN A61K031-47
R: AL AT BE BG CH CY CZ DE DK EE ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI SK TR
ADT WO 2003032921 A2 **WO 2002-US33246 20021016**; US 2004087657 A1 **Provisional US 2001-329705P 20011016, US 2002-273401 20021016**; EP 1443928 A2 **EP 2002-778601 20021016, WO 2002-US33246 20021016**
FDT EP 1443928 A2 Based on WO 2003032921
PRAI **US 2001-329705P 20011016; US 2002-273401 20021016**
IC ICM A61K000-00; A61K031-19; A61K031-47
ICS A61K031-16
AB WO2003032921 A UPAB: 20030703
NOVELTY - A method of inhibiting **histone deacetylase** in the brain of a mammal comprises administration of a **histone deacetylase** inhibitor (A) is used.
ACTIVITY - Cytostatic; Nootropic; Anticonvulsant; Neuroprotective; Antiparkinsonian; Neuroleptic; Cerebroprotective; Tranquilizer; Ophthalmological.
MECHANISM OF ACTION - **Histone Deacetylase** (HDAC) Inhibitor.
Test details are described but no biological data is given.
USE - For inhibition of **histone deacetylase** in the brain of a mammal; for treating central nervous system diseases including polyglutamine expansion disease e.g. Huntington's disease in mammal e.g. human, brain cancer (all claimed), inherited neurodegenerative disease e.g. Alzheimer's disease, senile dementia, Pick's disease (lobar atrophy), Huntington's disease, multiple system atrophy combining dementia with ataxia and manifestations of Parkinson's disease, progressive supernuclear palsy (Steel-Richardson-Olszewski), diffuse Lewy Body disease, corticodentatonigral degeneration, Hallervorden-Spatz disease, progressive familial myoclonic epilepsy, paralysis agitans (Parkinson's disease), striatonigral degeneration, torsion dystonia (torsion spasm, dystonia musculorum deformans), spasmodic torticollis and other dyskinesis, familial tremor, Gilles de la Tourette syndrome, cerebellar cortical degeneration, olivopontocerebellar atrophy (OPCA), Friedreich's ataxia and related disorders, central autonomic nervous system failure (Shy-Drager syndrome), muscular weakness and wasting without sensory changes (motor neuron disease), amyotrophic lateral sclerosis, infantile spinal muscular atrophy (Werdnig-Hoffman), juvenile spinal muscular atrophy, (Wohlfart-Kugelberg-Welender), primary lateral sclerosis, hereditary spastic paraplegia, peroneal muscular atrophy (Charcot-Marie-Tooth), hypertrophic interstitial polyneuropathy (Dejerine-Sottas), chronic progressive neuropathy, pigmentary degeneration of retina (retinitis pigmentosa) and hereditary optic atrophy (Leber's

disease).
ADVANTAGE - (A) Can cross the blood brain barrier to significantly inhibit HDAC activity causing the accumulation of acetylated histones in the brain.
Dwg.0/2
FS CPI
FA AB; GI; DCN
MC CPI: B06-D02; B06-D03; B06-D09; B07-D04C; B07-D05; B07-F01; B10-A18; B10-C02; B10-C04; B10-D03; B10-G02; B14-D07A; B14-H01; B14-J01A3; B14-J01A4; B14-J01B3; B14-J01B4; **B14-N03**
TECH UPTX: 20030703
TECHNOLOGY FOCUS - ORGANIC CHEMISTRY - Preferred Compound: (A) is octanedioic acid hydroxyamide phenylamide (Ia), octanedioic acid hydroxyamide 3-pyridylamide (Ib), N-hydroxy-3-(3-(hydroxyamino)-3-oxo-1-propenyl)-benzamide (Ic) or a compound of formula (II)-(XII).
R3, R4 = H, OH, optionally substituted alkyl, cycloalkyl, alkenyl, arylalkyloxy, aryloxy or pyridine;
R3+R4 = piperidine;
R2 = hydroxylamino, OH, amino, alkylamino, dialkylamino or alkyloxy;
n = 4-8;
X, Y = OH, amino, hydroxylamino, optionally substituted alkyloxy, alkylamino, dialkylamino, arylamino, alkylarylamino, alkyloxyamino, aryloxyamino, alkyloxyalkylamino or aryloxyalkylamino;
R = H, OH, alkyl (optionally substituted), arylalkyloxy or aryloxy;
m, n', o = 0-8;
R1, R2a = H, OH, optionally substituted alkyl, aryl, alkyloxy or aryloxy;
Ra = optionally substituted phenyl, piperidine, thiazole, 2-pyridine, 3-pyridine or 4-pyridine;
A = amide moiety;
R1a, R2b = optionally substituted aryl, naphtha, pyridineamino, 9-purine-6-amine, thiazoleamino, aryloxy, arylalkyloxy or pyridine;
n'' = 3-10;
L = -(CH2)n''-, -(CH=CH)m'-, phenyl and/or cycloalkyl;
m' = 0-10;
R7, R8 = optionally substituted aryl, naphthyl, pyridineamino, 9-purine-6-amine, thiazoleamino, aryloxy, arylalkyloxy or pyridine;
R4a = H, halo, phenyl or cycloalkyl;
Ya = naphthyl-1-yl, quinolin-4-yl, isoquinolin-4-yl, quinolin-5-yl, isoquinolin-5-yl, naphthyl-2-yl or quinolin-6-yl;
R7a = quinolin-8-yl, quinolin-7-yl, 9H-purin-9-yl, 1,2,3,4-tetrahydro-naphthalen-1-yl or pteridin-4-yl; and
R2c = aryl, naphthyl, aryloxy, arylalkyloxy (all optionally substituted), pyridineamino, 9-purine-6-amine, thiazoleamino or pyridine.
ABEX UPTX: 20030703
SPECIFIC COMPOUNDS - 4 Compounds are specifically claimed as (A) e.g. suberoylanilide hydroxamic acid (SAHA) (octanedioic acid hydroxyamide phenylamide) (Ia).

ADMINISTRATION - Administration of (A) is 2-2000, preferably 400-1200 mg/day orally in 1-4 divided doses, or 3-1500 mg/m2/day intravenously (including bolus or infusion), subcutaneously or intramuscularly (as depot injections or implants), intraperitoneally or intranasally.

EXAMPLE - None given.

L61 ANSWER 20 OF 28 WPIX COPYRIGHT 2004 THOMSON DERWENT on STN
AN 2003-430347 [40] WPIX
DNC C2003-113775
TI Enhancing progenitor cell differentiation and regeneration or differentiation-related gene expression in a progenitor cell, useful for treating tissue degeneration, comprises contacting the cell with a deacetylase inhibitor.
DC B04 D16

IN PURI, P L; SARTORELLI, V
PA (SALK) SALK INST BIOLOGICAL STUDIES; (USSH) US DEPT HEALTH & HUMAN SERVICES
CYC 101
PI WO 2003033678 A2 20030424 (200340)* EN 40 C12N000-00
RW: AT BE BG CH CY CZ DE DK EA EE ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SK SL SZ TR TZ UG ZM ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT RO RU SD SE SG SI SK SL TJ TM TN TR TT TZ UA UG US UZ VC VN YU ZA ZM ZW
ADT WO 2003033678 A2 **WO 2002-US33570 20021017**
PRAI **US 2001-343854P 20011025; US 2001-335705P 20011018**
IC ICM C12N000-00
AB WO2003033678 A UPAB: 20030624
NOVELTY - Enhancing progenitor cell differentiation or differentiation-related gene expression in a progenitor cell, comprises contacting an undifferentiated progenitor cell with an amount of a deacetylase inhibitor for a period of time sufficient to induce progenitor cell differentiation or enhance expression of the genes.

DETAILED DESCRIPTION - AN INDEPENDENT CLAIM is included for the method of treating a disease or condition associated with degeneration of muscle tissue, nerve tissue or hematopoietic tissue, or a deficiency in myogenesis, neurogenesis or hematopoiesis, comprising identifying a subject suffering a disease or condition associated with degeneration of muscle tissue, nerve tissue or hematopoietic tissue, or a subject deficient in myogenesis, neurogenesis or hematopoiesis; and administering to the subject an amount of a deacetylase inhibitor to induce differentiation of progenitor cells which mature into muscle tissue, nerve tissue or hematopoietic tissue.

ACTIVITY - Neuroprotective; Immunomodulator; Dermatological; Nootropic; Antiparkinsonian; Antianemic; Cytostatic; Anti-HIV; Protozoacide; Vulnerary.

No biological data given.

MECHANISM OF ACTION - Deacetylase-Inhibitor.

No biological data given.

USE - The method is useful in promoting cell differentiation and regeneration using deacetylase inhibitors. The method is used to inhibit, prevent or treat diseases or conditions associated with a degeneration or loss of tissue, such as muscle tissue, nerve tissue or hematopoietic tissue.

In particular, the disease or condition is muscular atrophy, muscular dystrophy, muscular cachexia, dermatomyositis, Alzheimer's disease, olivopentocerebellar atrophy, Parkinson's disease, degeneration of nervous tissue, ocular atrophy, hepatocerebral degeneration, idiopathic aplastic anemia, secondary aplastic anemia, amyotrophic lateral sclerosis, poliomyelitis, bone marrow loss induced by radiation therapy or chemotherapy, multiple myeloma, acute lymphocytic leukemia, HIV infection, AIDS, malaria, chronic myelogenous leukemia, Fanconi's anemia or trauma (claimed).

Dwg.0/10
FS CPI
FA AB; DCN
MC CPI: B04-C01; B04-F02; B04-N04; B05-A01B; B10-B02F; B10-C04E; B14-A02B1; B14-A03B; B14-C03; B14-D07; B14-F03; B14-H01A; B14-J01; B14-J05; B14-N01; **B14-N03**; B14-N17C; D05-H08
TECH UPTX: 20030624
TECHNOLOGY FOCUS - BIOTECHNOLOGY - Preferred Method: Enhancing progenitor cell differentiation further comprises, once progenitor cell differentiation has been induced, removing an amount of the deacetylase inhibitor sufficient to allow further differentiation of the

differentiated progenitor cell to occur. The progenitor cell is a muscle progenitor cell or myoblast, a neuronal progenitor cell or neuroblast, or a hematopoietic progenitor cell. The progenitor cell comprises a cell culture and is located within an organism. It is a mammalian progenitor cell, particularly human progenitor cell. The deacetylase inhibitor is an inhibitor of **histone deacetylase**, particularly HDAC1.
The deacetylase inhibitor may also be sodium butyrate, trichostatin A, valproic acid, or any of their combinations. The method is a method of enhancing myogenesis, neurogenesis, hematopoiesis, or any of their combinations. The method further comprises introducing an Rb or pRb protein into the cell. In enhancing differentiation-related gene expression in a progenitor cell, contacting the myoblast with the agent or the deacetylase inhibitor enhances expression of muscle-specific genes. By inhibiting HDAC1, the inhibitor interferes with the HDAC1/MyoD interaction in the myoblast. The deacetylase inhibitor is administered to a human subject in an amount to increase the rate of differentiation of a progenitor cell within the subject. The subject is deficient in myogenesis, neurogenesis and/or hematopoiesis, or is suffering a disease or condition associated with a loss of 2 or more of muscle tissue, nerve tissue, hematopoietic tissue, or their combinations.
In treating a disease or condition associated with degeneration of muscle tissue, nerve tissue or hematopoietic tissue, or a deficiency in myogenesis, neurogenesis or hematopoiesis, the deacetylase inhibitor further comprises a carrier, adjuvant, vehicle or salt. The method further comprises administering to the subject an Rb or pRb protein.

ABEX UPTX: 20030624

ADMINISTRATION - The deacetylase inhibitor is administered to provide plasma levels of about 10-500 mug/ml. Valproic acid may be given at a dosage of 15-60 mg/kg/day. Administration can be oral, parenteral (e.g. intravenous or intraperitoneal), rectal, topical, ophthalmic, nasal or transdermal.

L61 ANSWER 21 OF 28 WPIX COPYRIGHT 2004 THOMSON DERWENT on STN
AN 2002-740636 [80] WPIX
DNC C2002-209613
TI New carbamic acid compounds are **histone deacetylase** inhibitors used for treating e.g. cancer, Parkinson's disease, asthma, bacterial infection and Alzheimer's disease.
DC B05
IN AMOLINS, A; ANDRIANOV, V; BOKALDERE, R M; DIKOVSKA, K; DUFFY, J E S; FINN, P W; GAILITE, V; HARRIS, C J; KALVINSH, I; LOLYA, D; LOZA, E; MOORE, K G; RITCHIE, J; ROMERO-MARTIN, M; SEMENIKHINA, V; STARCHENKOV, I; VORONA, M; WATKINS, C J; BOKALDERE, R; ROMERO-MARTIN, M R; SEMINKHINA, V
PA (PROL-N) PROLIFIX LTD; (AMOL-I) AMOLINS A; (ANDR-I) ANDRIANOV V; (BOKA-I) BOKALDERE R; (DIKO-I) DIKOVSKA K; (DUFF-I) DUFFY J E S; (FINN-I) FINN P W; (GAIL-I) GAILITE V; (HARR-I) HARRIS C J; (KALV-I) KALVINSH I; (LOLY-I) LOLYA D; (LOZA-I) LOZA E; (MOOR-I) MOORE K G; (RITC-I) RITCHIE J; (ROME-I) ROMERO-MARTIN M R; (SEMI-I) SEMINKHINA V; (STAR-I) STARCHENKOV I; (VORO-I) VORONA M; (WATK-I) WATKINS C J
CYC 98
PI WO 2002026696 A1 20020404 (200280)* EN 346 C07C233-03 <--
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PH PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW
AU 2001090134 A 20020408 (200280) C07C233-03 <--
EP 1335898 A1 20030820 (200362) EN C07C233-03
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI TR
JP 2004509941 W 20040402 (200424) 620 C07C259-06
US 2004092598 A1 20040513 (200432) A61K031-44

ADT WO 2002026696 A1 **WO 2001-GB4329 20010927**; AU 2001090134 A **AU 2001-90134 20010927**; EP 1335898 A1 **EP 2001-970014 20010927, WO 2001-GB4329 20010927**; JP 2004509941 W **WO 2001-GB4329 20010927, JP 2002-531082 20010927**; US 2004092598 A1 **WO 2001-GB4329 20010927**, US 2003-381791 20030827

FDT AU 2001090134 A Based on WO 2002026696; EP 1335898 A1 Based on WO 2002026696; JP 2004509941 W Based on WO 2002026696

PRAI **US 2001-297785P 20010614; GB 2000-23985 20000929**

IC ICM A61K031-44; C07C233-03; C07C259-06

ICS A61K031-165; A61K031-166; A61K031-167; A61K031-19; A61K031-198; A61K031-216; A61K031-277; A61K031-341; A61K031-343; A61K031-381; A61K031-40; A61K031-4015; A61K031-4045; A61K031-405; A61K031-4184; A61K031-4245; A61K031-4402; A61K031-4409; A61P017-06; A61P035-00; A61P043-00; C07C233-05; C07C233-08; C07C233-09; C07C259-08; C07D207-337; C07D207-40; C07D207-46; C07D209-14; C07D209-22; C07D213-06; C07D213-56; C07D235-24; C07D271-08; C07D307-34; C07D307-54; C07D307-68; C07D317-60; C07D333-24; C07D333-60; C07D333-68; C07D403-12

AB WO 200226696 A UPAB: 20021212

NOVELTY - Carbamic acid compounds (I) are new.

DETAILED DESCRIPTION - Carbamic acid compounds of formula A-Q1-J-Q2-C(O)-NH-OH (I), their salts, solvates, amides, esters, ethers, chemically protected forms, and prodrugs, are new.

A = aryl (preferably 5-20C aryl (optionally substituted));

Q1 = aryl leader group having a backbone of at least 2 carbon atoms (preferably optionally substituted 1-7C alkylene);

J = -N(R1)-C(O)- or -C(O)-N(R1)-;

R1 = H, 1-7C alkyl, 3-20C heterocyclyl or 5-20C aryl;

Q2 = acid leader group having a backbone of at least 3C atoms (preferably 1-7C alkylene, 5-20C arylene, 5-20C arylene-1-7C alkylene or 1-7C alkylene-5-20C arylene (all optionally substituted)).

ACTIVITY - Cytostatic; Antipsoriatic; Antiarteriosclerotic; Vasotropic; Nootropic; Neuroprotective; Antiparkinsonian; Anticonvulsant; Antiinflammatory; Osteopathic; Antirheumatic; Antiarthritic; Antidiabetic; Ophthalmological; Antianemic; Fungicide; Antiparasitic; Protozoacide; Antibacterial; Virucide; Immunosuppressive; Hepatotropic; Dermatological; Antiallergic; Antiasthmatic.

MECHANISM OF ACTION - **Histone deacetylase** (HDAC) inhibitor.

In an assay, a source of HDAC (e.g. crude HeLa extract (2 mu l)) was incubated with radioactively labelled peptide (3 mu l) along with 2E-5,5-diphenylpenta-2,4-dienoic acid (5-hydroxycarbamoylpentyl)amide (Ia) (1.5 mu l) in a total volume of 150 mu l of buffer. The reaction was carried out at 37 deg. C for 1 hour, after which the reaction was stopped. Then, ethyl acetate (750 mu l) was added, the sample vortexed and after centrifugation, 600 mu l from the upper phase were transferred to a vial containing scintillation liquid (3 ml).

The activity of (Ia) for the HDAC inhibition was 95% at a rate of 500 nM.

USE - Used for treating proliferative conditions, cancer and psoriasis (claimed). (I) Are used for treating malignant neoplasms and tumors, leukemias, bone diseases, fibroproliferative disorders (e.g. liver fibrosis), atherosclerosis, restenosis, neurodegenerative disease (e.g. Alzheimer's disease, Parkinson's disease, Huntington's chorea, amyotropic lateral sclerosis, spiro-cerebellar degeneration), inflammatory disease (e.g. osteoarthritis, rheumatoid arthritis), disease involving angiogenesis (e.g. diabetic retinopathy), hematopoietic disorder (e.g. anaemia, sickle cell anaemia and thalassaemia), fungal infection, parasite infection (e.g. malaria, trypanosomiasis, helminthiasis, protozoal infection), bacterial infection, viral infection, condition treatable by immune modulation (e.g. multiple sclerosis, autoimmune diabetes, lupus, atopic dermatitis, allergies, asthma, allergic rhinitis, inflammatory

bowel disease and for improving grafting of transplants).
Dwg.0/0
FS CPI
FA AB; GI; DCN
MC CPI: B06-H; B07-H; B10-A18; B14-A01; B14-A02; B14-A03; B14-A03B; B14-A04; B14-B02; B14-C03; B14-C06; B14-C09; B14-F02; B14-F03; B14-F07; B14-F09; B14-G02; B14-G02A; B14-H01; B14-J01A3; B14-J01B3; B14-J07; B14-K01A; B14-N01; **B14-N03**; B14-N17
TECH UPTX: 20021212
TECHNOLOGY FOCUS - ORGANIC CHEMISTRY - Preparation: Preparation of (I) comprises e.g. reacting a carboxylic acid compound of formula (II) with an amine compound of formula (III) to give a compound of formula (IV) and reacting (IV) with NH2OH.
R = not defined.
ABEX UPTX: 20021212
WIDER DISCLOSURE - Also disclosed is a kit comprising (I) provided in a container and/or with packaging, and instructions for use.

SPECIFIC COMPOUNDS - 90 Compounds (I) are specifically claimed e.g: 2E-5,5-diphenylpenta-2,4-dienoic acid (5-hydroxycarbamoylpentyl)amide (Ia).

ADMINISTRATION - The dosage is 0.1-250 mg/kg/day orally, buccally, sublingually, transdermally, transmucosally, intranasally, ocularly, pulmonarily (by inhalation or insufflation), rectally, vaginally or parenterally (including subcutaneous, intradermal, intramuscular, intravenous, intraarterial, intracardial, intrathecal, intraspinal, intracapsular, subcapsular, intraorbital, intraperitoneal, intratracheal, subcuticular, intraarticular, subarachnoid and intrasternal route).

EXAMPLE - 1,1'-Carbonyldiimidazole (0.36 g) was added to a solution of 5,5-diphenyl-penta-2E,4E-dienoic acid (0.35 g) in dry tetrahydrofuran (10 ml) and the obtained mixture was stirred for 1 hour at ambient temperature. To the mixture triethylamine (0.30 g) and methyl 6-aminohexanoate hydrochloride (0.40 g) were added and the resultant suspension was stirred for 6 hours at ambient temperature. The solvent was removed, to the residue water (15 ml) was added and the precipitate was filtered off, washed and dried to give 2E-6-(5,5-diphenylpenta-2,4-dienoylamino)-hexanoic acid methyl ester (V) (84%).
A solution of sodium methylate (6 mmol) in methanol (5 ml) was added to a solution of hydroxylamine hydrochloride (0.28 g) in methanol (8 ml). The mixture was stirred for 10 minutes, and the precipitate was filtered off. (V) (0.30 g) was added to the filtrate and the mixture was heated. The resultant mixture was stirred for 4 hours at ambient temperature and the solvent was removed. The product was dissolved in water and worked up to give 2E-5,5-diphenylpenta-2,4-dienoic acid (5-hydroxycarbamoylpentyl)amide (91%).

DEFINITIONS - Preferred Definitions:
A = phenyl optionally substituted by G, pyridine, furan, indole, pyrrole, imidazole, naphthalene, quinoline, benzimidazole, benzothiofuran, fluorene, acridine and carbazole;
G = halo, methyl, ethyl, isopropyl, tert-butyl, cyano, trifluoromethyl, hydroxy, methoxy, ethoxy, isopropoxy, trifluoromethoxy, phenoxy, methylthio, trifluoromethylthio, hydroxymethyl, amino, dimethylamino, diethylamino, morpholino, amido, acetamide, acetyl, nitro, sulfonamido or phenyl;
R1 = H;
Q1 = CH=CH or CH=CH-CH=CH- (all optionally substituted by at least one halo, OH, OMe, OEt, OPr, Ph, or =O);
Q2 = (CH2)4-6, T-CH=CH, T'-CH=CH, or T-CH2-CH2;
T = 1,3-phenylene, and
T' = 1,4-phenylene.

L61 ANSWER 22 OF 28 WPIX COPYRIGHT 2004 THOMSON DERWENT on STN
AN 2002-454539 [48] WPIX
DNC C2002-129225
TI New carbamic acid derivatives, used to treat e.g. cancer, bone diseases, atherosclerosis, restenosis, Alzheimer's disease, anemia, fungal infections, multiple sclerosis and asthma, are **histone deacetylase** inhibitors.
DC B05
IN ANDRIANOV, V; DIKOVSKA, K; DUFFY, J E S; FINN, P W; GAILITE, V; HARRIS, C J; KALVINSH, I; LOZA, E; MOORE, K G; PISKUNOVA, I; RITCHIE, J; ROMERO-MARTIN, M; STARCHENKOV, I; VORONA, M; WATKINS, C J; ADRIANOV, V; CAROEN, A; ROMERO-MARTIN, M R; WATKINS, C
PA (PROL-N) PROLIFIX LTD; (ANDR-I) ANDRIANOV V; (DIKO-I) DIKOVSKA K; (DUFF-I) DUFFY J E S; (FINN-I) FINN P W; (GAIL-I) GAILITE V; (HARR-I) HARRIS C J; (KALV-I) KALVINSH I; (LOZA-I) LOZA E; (MOOR-I) MOORE K G; (PISK-I) PISKUNOVA I; (RITC-I) RITCHIE J; (ROME-I) ROMERO-MARTIN M R; (STAR-I) STARCHENKOV I; (VORO-I) VORONA M; (WATK-I) WATKINS C
CYC 98
PI WO 2002030879 A2 20020418 (200248)* EN 267 C07C311-21 <--
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PH PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW
AU 2001090131 A 20020422 (200254) C07C311-21 <--
EP 1328510 A2 20030723 (200350) EN C07C311-21
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI TR
JP 2004511462 W 20040415 (200426) 482 C07C311-08
US 2004077726 A1 20040422 (200428) A61K031-19
ADT WO 2002030879 A2 **WO 2001-GB4326 20010927**; AU 2001090131 A **AU 2001-90131 20010927**; EP 1328510 A2 **EP 2001-970011 20010927**, **WO 2001-GB4326 20010927**; JP 2004511462 W **WO 2001-GB4326 20010927**, **JP 2002-534267 20010927**; US 2004077726 A1 **WO 2001-GB4326 20010927**, US 2003-381790 20030820
FDT AU 2001090131 A Based on WO 2002030879; EP 1328510 A2 Based on WO 2002030879; JP 2004511462 W Based on WO 2002030879
PRAI **US 2001-308136P 20010730**; **GB 2000-23986 20000929**; **US 2001-297784P 20010614**
IC ICM A61K031-19; C07C311-08; C07C311-21
ICS A61K031-34; A61K031-341; A61K031-36; A61K031-40; A61K031-403; A61K031-44; A61K031-4406; A61P017-06; A61P035-00; A61P043-00; C07C311-10; C07C311-13; C07C311-16; C07C311-17; C07C311-19; C07C311-20; C07C311-29; C07C311-45; C07D209-82; C07D209-88; C07D213-42; C07D213-65; C07D213-71; C07D307-52; C07D317-58
AB WO 200230879 A UPAB: 20031107
NOVELTY - Carbamic acid compounds (I) are new.
DETAILED DESCRIPTION - Carbamic acid compounds of formula A-Q1-J-Q2-C(O)-NH-OH (I), their salts, solvates, amides, esters, ethers, chemically protected forms and prodrugs are new.
A = optionally substituted 5-20C aryl;
Q1 = covalent bond, or optionally substituted 1-7C alkylene;
J = -N(R1)-S(=O)2- or -S(=O)2-N(R1)-;
R1 = H, 1-7C alkyl, 3-20C heterocyclyl or 5-20C aryl; and
Q2 = 1-7C alkylene, 5-20C arylene, 5-20C arylene-1-7C alkylene 1-7C alkylene-5-20C arylene (all optionally substituted).
Provided that if J is -S(=O)2-N(R1)-, then Q1 is an aryl leade group.
An INDEPENDENT CLAIM is also included for use of (I) for the manufacture of a medicament for use in the treatment of a conditi mediated by **histone deacetylase** (HDAC).

ACTIVITY - Cytostatic; Antipsoriatic; Antiarteriosclerotic; Vasotropic; Nootropic; Neuroprotective; Antiparkinsonian; Anticonvulsant; Antiinflammatory; Osteopathic; Antirheumatic; Antiarthritic; Antidiabetic; Ophthalmological; Antianemic; Fungicide; Antiparasitic; Antimalarial; Protozoacide; Antibacterial; Antiviral; Immunosuppressive; Dermatological; Antiallergic; Antiasthmatic.

MECHANISM OF ACTION - **Histone deacetylase** (HDAC) inhibitor. A source of HDAC (e.g. crude HeLa extract (2 mu l)) was incubated with radioactively labelled peptide (3 mu l) along with 6-(2-phenylethenesulfonylamino)-hexanoic acid hydroxyamide (A) (1.5 mu l) in a total volume of 150 mu l of buffer. The reaction was carried out at 37 deg. C for 1 hour, after which the reaction was stopped. Then, ethyl acetate (750 mu l) was added, the sample vortexed and after centrifugation, 600 mu l from the upper phase were transferred to a vial containing scintillation liquid (3 ml). The % activity of (A) for the HDAC inhibition was 73% at the rate of 500 nM.

USE - For the manufacture of medicament useful in the treatment of conditions mediated by HDAC, proliferative condition, cancer and psoriasis of the human or animal body (claimed); in the treatment of malignant neoplasms and tumors, leukemias, bone diseases, fibroproliferative disorders (e.g. liver fibrosis), atherosclerosis, restenosis, neurodegenerative disease (e.g. Alzheimer's disease, Parkinson's disease, Huntington's chorea, amyotropic lateral sclerosis, spiro-cerebellar degeneration), inflammatory disease (e.g. osteoarthritis, rheumatoid arthritis), disease involving angiogenesis (e.g. diabetic retinopathy), haematopoietic disorder (e.g. anemia, sickle cell anemia, thalassaeimia), fungal infection, parasite infection (e.g. malaria, trypanosomiasis, helminthiasis, protozoal infection), bacterial infection, viral infection, condition treatable by immune modulation (e.g. multiple sclerosis, autoimmune diabetes, lupus, atopic dermatitis, allergies, asthma, allergic rhinitis, inflammatory bowel disease; and for improving grafting of transplants).

Dwg.0/0

FS CPI

FA AB; GI; DCN

MC CPI: B06-H; B07-H; B10-A08; B14-A01; B14-A02; B14-A04; B14-B02; B14-C09; B14-D07A; B14-F01G; B14-F03; B14-G02C; B14-G03; B14-H01A; B14-H01B; B14-J01A3; B14-J01A4; B14-N01; **B14-N03**; B14-N17C; B14-S01; B14-S04

ABEX UPTX: 20020730

WIDER DISCLOSURE - Also disclosed is a kit comprising (I) provided as a composition in a container and/or with packaging; and instruction for use.

SPECIFIC COMPOUNDS - Fifty five compounds (I) are specifically claimed e.g. 6-(2-phenylethenesulfonylamino)-hexanoic acid hydroxyamide (PX-117429) of formula (Ia).

ADMINISTRATION - The compounds are administered orally, buccally, sublingually, transdermally, transmucosally, intranasally, ocularly, pulmonarily (by inhalation or insufflation), rectally, vaginally, parenterally (including subcutaneous, intradermal, intramuscular, intravenous, intraarterial, intracardial, intrathecal, intraspinal, intracapsular, subcapsular, intraorbital, intraperitoneal, intratracheal, subcuticular, intraarticular, subarachnoid and intrasternal route), in a dosage of 0.1 - 250 mg/kg of body weight per day.

EXAMPLE - 2-Phenyl-ethenesulfonyl chloride (0.88 g) was added to a mixture of methyl 6-hexanoate hydrochloride (1.82 g) in acetonitrile (10 ml) and sodium carbonate (2.6 g) in water (10 ml). The mixture was stirred for 6 hours at room temperature. The product was extracted, dried and solvents were removed under reduced pressure. The product was chromatographed to give 6-(E-2-phenylethenesulfonylamino)-hexanoic acid methyl ester (a) (56 %). A solution of sodium methylate (6 mmole) in methanol (5 ml) was added

to a solution of hydroxylamine hydrochloride (0.28 g) in methanol (8 ml). The mixture was stirred for 10 minutes, and the precipitate was filtered off. (a) (0.30 g) was added to the filtrate and the mixture was heated. The resultant mixture was stirred for 4 hours at ambient temperature and the solvent was removed. The product was dissolved in water and worked up to give 6-(2-phenylethenesulfonylamino)-hexanoic acid hydroxyamide (62 %).

DEFINITIONS - Preferred Definitions:
A = phenyl (optionally substituted by G), pyridine, furan, indole, pyrrole, imidazole, naphthalene, quinoline, benzimidazole, benzothiofuran, fluorene, acridine or carbazole;
G = halo, methyl, ethyl, isopropyl, tert-butyl, cyano, trifluoromethyl, hydroxy, methoxy, ethoxy, isopropoxy, trifluoromethoxy, phenoxy, methylthio, trifluoromethylthio, hydroxymethyl, amino, dimethylamino, diethylamino, morpholino, amido, acetamide, acetyl, nitro, sulfonamido or phenyl;
R1 = H;
Q1 = -CH2-, -CH2CH2-, -CH2CH2CH2-, -CH=CH- or -CH=CH-CH=CH- (all optionally substituted with at least one halo, OH, -OMe, -OEt, -OPr, -Ph, or =O);
Q2 = phenylene-meta-ethylene group.

L61 ANSWER 23 OF 28 WPIX COPYRIGHT 2004 THOMSON DERWENT on STN
AN 2002-435186 [46] WPIX
DNC C2002-123567
TI New carbamic acid compounds are **histone deacetylase** inhibitors used for treating e.g. cancer, asthma, Parkinson's disease, bacterial infection and Alzheimer's disease.
DC B05
IN BOKALDERE, R M; DUFFY, J E S; FINN, P W; HARRIS, C J; KALVINSH, I; LOLYA, D; LOZA, E; ROMERO MARTIN, M R; SEMENIKHINA, V; STARCHENKOV, I; WATKINS, C J
PA (PROL-N) PROLIFIX LTD
CYC 97
PI WO 2002026703 A1 20020404 (200246)* EN 125 C07C323-60 <--
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PH PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW
AU 2001090132 A 20020408 (200252) C07C323-60 <--
ADT WO 2002026703 A1 **WO 2001-GB4327 20010927**; AU 2001090132 A **AU 2001-90132 20010927**
FDT AU 2001090132 A Based on WO 2002026703
PRAI **GB 2000-23983 20000929**
IC ICM C07C323-60
ICS A61P017-06; A61P035-00; C07C259-06
AB WO 200226703 A UPAB: 20020722
NOVELTY - Carbamic acid compounds (I) are new.
DETAILED DESCRIPTION - Carbamic acid compounds of formula A-Q1-J-R2-X-R3-C(O)-NH-OH (I), their salts, solvates, amides, esters, ethers, chemically protected forms, and prodrugs are new.
A = aryl (preferably optionally substituted 5-20C aryl);
Q1 = aryl leader group having a backbone of at least 2 carbon atom (preferably optionally substituted 1-7C alkylene), or a covalent bond;
J = N(R1)-C(O) or C(O)-N(R1);
R1 = H, 1-7C alkyl, 3-20C heterocyclyl or 5-20C aryl;
X = O or S, and
R2, R3 = 1-7C alkylene, 5-20C arylene, 5-20C arylene-1-7C alkylene or 1-7C alkylene-5-20C arylene (all optionally substituted).
ACTIVITY - Cytostatic; Antipsoriatic; Antiarteriosclerotic; Vasotropic; Nootropic; Neuroprotective; Antiparkinsonian; Anticonvulsant;

Antiinflammatory; Osteopathic; Antirheumatic; Antiarthritic; Antidiabetic; Ophthalmological; Antianemic; Fungicide; Antiparasitic; Protozoacide; Antibacterial; Virucide; Immunosuppressive; Hepatotropic; Dermatological; Antiallergic; Antiasthmatic.

MECHANISM OF ACTION - **Histone deacetylase** (HDAC) inhibitor.

A source of HDAC (e.g. crude HeLa extract (2 mu l) was incubated with radioactively labeled peptide (3 mu l) along with (2E)(4E)-5-phenylpenta-2,4-dienoic acid((2-(2-hydroxycarbamoylethylsulfanyl)ethyl)amide (Ia) (1.5 mu l) in a total volume of 150 mu l of buffer. The reaction was carried out at 37 deg. C for 1 hour, after which the reaction was stopped. Then, ethyl acetate (750 mu l) was added, the sample vortexed and after centrifugation, 600 mu l from the upper phase were transferred to a vial containing scintillation liquid (3 ml). The activity of (Ia) for HDAC inhibition was 95% at a rate of 500 nM.

USE - Used for treating proliferative conditions, cancer and psoriasis (claimed). (I) Are used for treating malignant neoplasm and tumors, leukemia, bone diseases, fibroproliferative disorders (e.g. liver fibrosis), atherosclerosis, restenosis, neurodegenerative disease (e.g. Alzheimer's disease, Huntington's chorea, amyotropic lateral sclerosis, spiro-cerebellar degeneration), inflammatory disease (e.g. osteoarthritis, rheumatoid arthritis), disease involving angiogenesis (e.g. diabetic retinopathy), hematopoietic disorder (e.g. anemia, sickle cell anemia, thalassaemia), fungal infection, parasitic infection (e.g. malaria, trypanosomiasis, helminthiasis, protozoal infection), bacterial infection, viral infection, condition treatable by immune modulation (e.g. multiple sclerosis, autoimmune diabetes, lupus, atopic dermatitis, allergies, asthma, allergic rhinitis, inflammatory bowel disease; and for improving grafting of transplants).

Dwg.0/0

FS CPI

FA AB; GI; DCN

MC CPI: B07-H; B10-A18; B14-A01; B14-A02; B14-A03B; B14-A04; B14-B02; B14-C03; B14-C06; B14-C09; B14-D07A; B14-F02; B14-F07; B14-F09; B14-H01; B14-J01; B14-J07; B14-N01; **B14-N03**; B14-N17; B14-S04

TECH UPTX: 20020722

TECHNOLOGY FOCUS - ORGANIC CHEMISTRY - Preparation: None given in the source material.

ABEX UPTX: 20020722

WIDER DISCLOSURE - Also disclosed is a kit comprising (I) provided as a composition in a container and/or with packaging; and instruction for use.

SPECIFIC COMPOUNDS - 8 Compounds (I) are specifically claimed e.g: (2E)(4E)-5-phenylpenta-2,4-dienoic acid((2-(2-hydroxycarbamoylethylsulfanyl)ethyl)amide (Ia).

ADMINISTRATION - The dosage is 0.1-250 mg/kg/day orally, buccally, sublingually, transdermally, transmucosally, intranasally, ocularly, pulmonarily (by inhalation or insufflation), rectally, vaginally or parenterally (including subcutaneous, intradermal, intramuscular, intravenous, intraarterial, intracardial, intrathecal, intraspinal, intracapsular, subcapsular, intraorbital, intraperitoneal, intratracheal, subcuticular, intraarticular, subarachnoid and intrasternal route).

EXAMPLE - 1,1'-Carbonyldimidazole (0.36 g) was added to a solution of 5-phenyl-penta-2E,4E-dienoic acid (0.35 g) in dry tetrahydrofuran (10 ml) and the obtained mixture was stirred for 1 hour at ambient temperature. To the mixture triethylamine (0.30 g) and methyl 3-(2-amino-ethylsulfanyl)-propionate hydrochloride (2.2 mmol) were added and the resultant suspension was stirred for 6 hours at ambient temperature. The solvent was removed, to the residue water (15 ml) was added and the precipitate was filtered off, washed and dried to give 3-(2-((2E)(4E)-5-phenylpenta-2,4-

dienoylamino)ethylsulfanyl)propionic acid methyl ester (II) (67%).
A solution of sodium methylate (6 mmol) in methanol (5 ml) was added to a solution of hydroxylamine hydrochloride (0.28 g) in methanol (8 ml). A mixture was stirred for 10 minutes, and the precipitate was filtered off. (II) (1 mmol) was added to the filtrate and the mixture was heated. The resultant mixture was stirred for 4 hours at ambient temperature and the solvent was removed. The product was dissolved in water and worked up to give (2E)(4E)-5-phenylpenta-2,4-dienoic acid((2-(2-hydroxycarbamoylethylsulfanyl)ethyl)amide (47%).

DEFINITIONS - Preferred Definitions:
A = phenyl optionally substituted by G, pyridine, furan, indole, pyrrole, imidazole, naphthalene, quinoline, benzimidazole, benzothiofuran, fluorene, acridine or carbazole;
G = halo, methyl, ethyl, isopropyl, tert-butyl, cyano, trifluoromethyl, hydroxy, methoxy, ethoxy, isopropoxy, trifluoromethoxy, phenoxy, methylthio, trifluoromethylthio, hydroxymethyl, amino, dimethylamino, diethylamino, morpholino, amido, acetamide, acetyl, nitro, sulfonamido or phenyl;
R1 = H;
Q1 = CH2, CH=CH or CH=CH-CH=CH (all optionally substituted by halo, OMe, OEt, OPr, Ph, or =O);
R2, R3 = phenylene-methylene, phenylene-ethylene, phenylene-propylene or phenylene-ethenylene;
R2-X-R3 = CH2-S-(CH2)1-5-, -CH2-O-(CH2)1-5-, -(CH2)2-5-S-CH2-, -(CH2)2-5-O-CH2-, -(CH2)3-O-(CH2)2-3-, -(CH2)2-S-(CH2)2-3-, -(CH2)4-S-(CH2)2-, -(CH2)4-O-(CH2)2-, -(CH2)3-O-T'-CH2- or -T-O-CH2-;
T = 1,3-phenylene, and
T' = 1,4-phenylene.

L61 ANSWER 24 OF 28 WPIX COPYRIGHT 2004 THOMSON DERWENT on STN
AN 2002-217052 [27] WPIX
DNC C2002-066383
TI Novel 47508 polypeptide, a member of human **histone deacetylase** family, useful for treating or preventing e.g. leukemia, aplastic anemia, diabetes, obesity, osteoporosis, pulmonary embolism and dysentery.
DC B04 D16
IN MEYERS, R A
PA (MILL-N) MILLENNIUM PHARM INC; (MEYE-I) MEYERS R A
CYC 95
PI WO 2002008273 A2 20020131 (200227)* EN 118 C07K014-435 <--
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW
AU 2001077105 A 20020205 (200236) C07K014-435 <--
US 2002164752 A1 20021107 (200275) C12Q001-68 <--
ADT WO 2002008273 A2 **WO 2001-US23153 20010723**; AU 2001077105 A **AU 2001-77105 20010723**; US 2002164752 A1 **Provisional US 2000-220008P 20000721, US 2001-911150 20010723**
FDT AU 2001077105 A Based on WO 2002008273
PRAI **US 2000-220008P 20000721; US 2001-911150 20010723**
IC ICM C07K014-435; C12Q001-68
ICS C07H021-04; C07K016-40; C12N005-06; C12N009-16; C12P021-02; G01N033-53
AB WO 200208273 A UPAB: 20020429
NOVELTY - An isolated 47508 polypeptide (I) (member of human **histone deacetylase** family) having a fully defined sequence of 413 amino acids (S2) as given in the specification, is new.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:

(1) an isolated nucleic acid (II) comprises a fully defined sequence of 1579 (S1) or 1242 (S3) nucleotides as given in specification, or its complement, encoding a polypeptide comprising a sequence of (S2);

(2) a host cell (III) which contains (II);

(3) an antibody (IV) or its antigen binding fragment which selectively binds (I);

(4) preparation of (I);

(5) detecting (M1) presence of (II) in a sample by contacting sample with nucleic acid probe or primer which selectively hybridizes to (II) and determining whether the nucleic acid probe or primer binds to a nucleic acid molecule in the sample;

(6) a kit comprising a compound which selectively binds to (I), or a nucleic acid probe which selectively hybridizes with (II), and instructions for use;

(7) modulating (M2) activity of (I) by contacting (I) or cell expressing (I) with compound which binds to the polypeptide in sufficient concentration to modulate the activity of the polypeptide;

(8) inhibiting (M3) aberrant activity of 47508-expressing cell by contacting a cell with a compound which modulates the activity or expression of (I); and

(9) treating or preventing (M4) a disorder characterized by aberrant activity of 47508-expressing cell in a subject by administering a compound that modulates activity or expression of (I) to a subject.

ACTIVITY - Cytostatic; antiinflammatory; antiasthmatic; respiratory-Gen; thrombolytic; antidiarrheic; osteopathic; antianemic; ophthalmological; virucide; immunosuppressive; analgesic; anorectic; antidiabetic; hepatotropic; vulnerary. No biodata is given in the source material.

MECHANISM OF ACTION - Activity or expression of 47508 protein or nucleic acid, modulator; gene therapy.

USE - (I) is useful for identifying a compound which binds to it. (IV) is useful for detecting presence of (I) in a sample. (M4) is useful for treating or preventing a disorder characterized by aberrant activity of 47508-expressing cell (all claimed). (I) is useful for treating disorders characterized by insufficient or excessive production of 47508 substrate or 47508 proteins, and for screening naturally occurring 47508 substrates. (I) is also useful for evaluating a compound for its ability to interact with 47508 polypeptide, and thus to identify natural or synthetic inhibitors of 47508 polypeptide. (II) is useful for expressing (I), and in gene therapy applications. Portions or fragments of (II) are useful to map their respective genes on a chromosome, e.g., to locate gene regions associated with genetic disease or to associate 47508 with a disease, identify individual from a minute biological sample (tissue typing), aid in forensic identification of a biological sample, and as probes or primers. (IV) is useful for isolating (I), detecting (I), evaluating abundance and pattern of expression of (I), to diagnostically monitor protein levels in tissue and to determine the efficacy of a given treatment regimen. (IV) is also useful for regulating bioavailability of 47508 proteins. (I), (II) and (IV) are useful for screening assays, predictive medicine (e.g., diagnostic assays, prognostic assays, monitoring clinical trials, and pharmacogenetics); and methods of treatment (e.g., therapeutic and prophylactic). (I), (II) and (IV) are also useful as markers of disorders of disease states, as markers for precursors or predisposition of disease states, as markers of drug activity or as markers of pharmacogenomic profile of a subject. (I) and (II) are useful for evaluating the efficacy of treatment of a disorder, and for evaluating efficacy of therapeutic or prophylactic agent. 47508 polypeptides and polynucleotides act as novel diagnostic targets and therapeutic agents for controlling cellular proliferative and/or differentiative disorders (including cancer e.g., carcinoma, sarcoma, or hematopoietic neoplastic disorder e.g., leukemias), disorders of breast

e.g., acute mastitis and fat necrosis; ovary e.g., choriocarcinoma and hill cell tumors; lung e.g., pulmonary embolism and bronchial asthma, or (d) colon e.g., diarrhea and dysentery, Crohn's disease, and also disorders associated with bone metabolism e.g., osteoporosis and steatorrhea; immune disorders e.g., keratoconjunctivitis, and aplastic anemia; viral diseases e.g., virus associated carcinoma especially hepatocellular cancer; and pain or metabolic disorders e.g., obesity, diabetes, hyperalgesia; and liver disorders e.g., hepatocellular necrosis or injury induced by agents including processes which disturb homeostasis, and liver injury caused by administration of various chemicals or drugs.
Dwg.0/3

FS CPI

FA AB; DCN

MC CPI: B04-E02E; B04-E02F; B04-E03E; B04-E03F; B04-E05; B04-F0100E; B04-G01; B11-C08E5; B12-K04A; B12-K04F; B14-A02; B14-C01; B14-C03; B14-E02; B14-E12; B14-F03; B14-F04; B14-G02; B14-H01; B14-K01; B14-K01A; B14-N01; **B14-N03**; B14-N12; B14-N17B; B14-S03A; B14-S04; D05-H09; D05-H11; D05-H12A; D05-H12D1; D05-H14; D05-H18

TECH UPTX: 20020429

TECHNOLOGY FOCUS - BIOTECHNOLOGY - Preparation: (I) is prepared by culturing (III) under conditions in which the nucleic acid molecule is expressed (claimed).
Preferred Nucleic Acid: (II) further comprises vector nucleic acid sequences and/or nucleic acid sequence encoding heterologous polypeptide.
Preferred Polypeptide: (I) further comprises heterologous amino acid sequence.
Preferred Method: In (M1), a sample comprising mRNA molecules is contacted with a nucleic acid probe. In (M3), a compound such as a peptide, phosphopeptide, a small organic molecule or an antibody is administered to a subject to reduce or inhibit the aberrant activity of a 47508-expressing cell located in cancerous or precancerous tissue.

ABEX UPTX: 20020429

WIDER DISCLOSURE - The following are disclosed:
(1) isolated nucleic acid molecules that are substantially identical to (S1) or (S3);
(2) nucleic acid molecules which hybridize under stringent hybridization condition to (S1) or (S3);
(3) an amino acid sequence that is substantially identical to (S2);
(4) an amino acid sequence encoded by nucleic acid molecule having nucleotide sequence which hybridizes under stringent conditions to (S1) or (S3);
(5) nucleic acid constructs and vectors that comprise 47508 nucleic acid molecule;
(6) isolated nucleic acid molecules which are antisense to 47508-encoding nucleic acid;
(7) fusion proteins comprising 47508 polypeptide fused to non-47508 polypeptides;
(8) screening for compounds that modulate the expression of 47508 nucleic acid expression and modulating 47508 nucleic acid expression using the screened compounds;
(9) assays for determining the presence or absence of a genetic alteration in 47508 polypeptide or nucleic acid molecule;
(10) a two dimensional array having several addresses, each of which is positionally distinguishable from each other address of the set, and each address of the set having a unique capture probe that may be a nucleic acid (a probe complementary to (II)) or a polypeptide, e.g., an antibody specific for (I);
(11) use of the array for analyzing the sample;
(12) nucleic acid molecules that differ from (II) due to degeneracy of genetic code;
(13) nucleic acid molecules encoding other 47508 family members which have a nucleotide sequence that differs from (S1) or (S3);
(14) molecular beacon oligonucleotide primer and probe molecules having a

region which is complementary to 47508 nucleic acid molecule, two complementary regions one having a fluorophore and one a quencher such that the molecular beacon is useful for quantitating the presence of (II);
(15) variants of 47508 polypeptide which functions as agonist or antagonist;
(16) making a 47508 polypeptide e.g., a peptide having non-wildtype activity or making a fragment or analog of 47508 polypeptide involves altering the sequence of the polypeptide e.g., the substitution or deletion of one or more amino acid residues of a 47508 polypeptide and testing the altered polypeptide for desired activity;
(17) a nucleic acid (N) which encodes (IV);
(18) vectors including (N) and cells transformed with (N) which are useful for producing the antibody;
(19) hybridomas which make (IV) and methods of using the cells for making (IV);
(20) non-human transgenic animals in which an endogenous 47508 gene has been altered by homologous recombination between an endogenous gene and an exogenous DNA molecule introduced into a cell of the animal;
(21) population of cells from the transgenic animal;
(22) novel agents identified by screening methods involving (I);
(23) a computer medium having executable code for receiving a subject expression profile; access a database of reference expression profile and either selecting a matching reference profile most similar to the subject expression profile or determining at least one comparison score for the similarity of the subject expression profile to at least one reference profile;
(24) a computer medium having several digitally encoded data records each of which includes a value representing level of expression of 47508 in a sample and a descriptor of the sample;
(25) an array having several addresses, each of which includes a unique polypeptide and at least one address of the array has a 47508 polypeptide disposed on it;
(26) a set of oligonucleotides, each of which is at least partially complementary to 47508 nucleic acid, useful for identifying single nucleotide polymorphisms;
(27) a machine-readable medium e.g., a magnetic, optical, chemical or mechanical information storage device provided with 47508 sequences;
(28) making a computer readable record of a sequence of a 47508 which includes recording the sequence on a computer readable matrix;
(29) a machine-readable medium for holding instructions for determining whether a subject has a 47508-associated disease or disorder or a predisposition to 47508-associated disease or disorder;
(30) an electronic system and/or a network for determining whether a subject has a 47508-associated disease or disorder or a predisposition to 47508-associated disease or disorder;
(31) a network for determining whether a subject has a 47508-associated disease or disorder or a predisposition to 47508-associated disease or disorder; and
(32) determining whether a subject has a 47508-associated disease or disorder or a predisposition to 47508-associated disease or disorder using the above mentioned network.
ADMINISTRATION - Pharmaceutical compositions comprising (I), (II), (IV) are administered by parenteral, e.g., intravenous, intradermal, subcutaneous, oral, transdermal, transmucosal or rectal route. Dosage of (I) ranges from 0.001-30 (preferably, 5-6) mg/kg body weight. (IV) is administered in dosages ranging from 0.1-10 mg/kg body weight. Modulator compounds identified using (I) are administered in dosages ranging from 1 microg-500 mg/kg (preferably, 1-50 microg/kg body weight).

EXAMPLE - Human 47508 sequence (a member of human **histone deacetylase** family) (S1) was 1579 nucleotides long. The region between and inclusive of the initiation codon and the termination codon was a methionine-initiated coding sequence of about 1242 nucleotides. The

coding sequence encoded a 413 amino acid (S2) protein. Endogenous human 47508 gene expression was determined using the Perkin-Elmer/ABI 7700 Sequence Detection System which employed TaqMan technology. 47508 was expressed in normal breast, ovary, lung, colon, liver, and endothelial cells, as well as tumors of the breast, ovary, lung, colon and liver. In most breast tumors analyzed, 47508 expression was elevated relative to that observed in normal breast tissue. In addition, a subset of ovary and lung tumors displayed an increase in 47508 expression, and all of the colon tumor samples displayed an increase in 47508 expression relative to the majority of normal colon tissue samples analyzed. Also a number of different lung cell lines expressed 47508, with neither the p16 or p53 tumor suppressor genes having a strong impact on 47508 expression under the conditions examined. Expression of 47508 was lowest in the H460 large cell lung carcinoma cells. Human 47508 had following regions or other structural features. A **histone deacetylase** domain (PFAM accession number PF00850) located at about amino acid residues 83 to 392 of (S2); a histidine deacetylase zinc-binding triad having two conserved aspartic acid residues, located at about amino acid residues 247 and 327 of (S2), and one conserved histidine residue, located at about amino acid residue 249 of (S2); a first charge-relay system formed by a conserved histidine residue, located at about amino acid residue 208 of (S2), and a conserved aspartic acid residue, located at about amino acid residue 245 of (S2); a second charge-relay system formed by a conserved histidine residue, located at about amino acid residue 209 of (S2), and a conservatively substituted asparagine residue, located at about amino acid residue 251 of (S2). Four Protein Kinase C phosphorylation sites, five Casein Kinase II phosphorylation sites; seven N-myristylation sites; and one amidation site (PS00009) located at about amino acid residues 356 to 359.

L61 ANSWER 25 OF 28 WPIX COPYRIGHT 2004 THOMSON DERWENT on STN
AN 2002-075165 [10] WPIX
CR 2002-034512 [04]; 2002-034538 [04]; 2002-066534 [09]; 2002-179352 [23]; 2002-607412 [65]
DNC C2002-022387
TI Modification of chromatin structure for facilitating transcription, replication and repair, comprises contacting chromatin with fusion molecule comprising DNA binding domain and component of a chromatin remodeling complex.
DC B04 D16
IN COLLINGWOOD, T; WOLFFE, A P; SNOWDEN, A; WOLFFE, E J
PA (SANG-N) SANGAMO BIOSCIENCES INC; (COLL-I) COLLINGWOOD T; (WOLF-I) WOLFFE A P; (SNOW-I) SNOWDEN A; (WOLF-I) WOLFFE E J
CYC 96
PI WO 2001083793 A2 20011108 (200210)* EN 99 C12N015-82 <--
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG UZ VN YU ZA ZW
AU 2001053914 A 20011112 (200222) C12N015-82 <--
US 2002115215 A1 20020822 (200258) C12Q001-68 <--
EP 1276859 A2 20030122 (200308) EN C12N015-10
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI TR
US 2003049649 A1 20030313 (200321) C12Q001-68
ADT WO 2001083793 A2 **WO 2001-US40616 20010427**; AU 2001053914 A **AU 2001-53914 20010427**; US 2002115215 A1 **Provisional US 2000-200590P 20000428, Provisional US 2000-228523P 20000828 , US 2001-844508 20010427**; EP 1276859 A2 **EP 2001-927467 20010427, WO 2001-US40616 20010427**; US 2003049649 A1 **Provisional US 2000-200590P 20000428, Provisional US**

2000-228523P 20000828, CIP of US 2001-844508 20010427, US 2002-84826 20020224

FDT AU 2001053914 A Based on WO 2001083793; EP 1276859 A2 Based on WO 2001083793

PRAI **US 2000-228523P 20000828; US 2000-200590P 20000428; US 2001-844508 20010427; US 2002-84826 20020224**

IC ICM C12N015-10; C12N015-82; C12Q001-68
ICS C07K014-47; C07K014-485; C07K014-505; C07K014-705; C07K014-72; C12N009-22; C12N015-62; C12N015-63; C12N015-67; C12N015-87

AB WO 200183793 A UPAB: 20030328
NOVELTY - Modifying (M1) a region of interest in cellular chromatin, comprises contacting the cellular chromatin with a fusion molecule that binds to a binding site in the region of interest, where the fusion molecule comprises a DNA binding domain and a component of a chromatin remodeling complex or its functional fragment, which modifies the region of interest.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:

(1) a fusion polypeptide (I) comprising a DNA binding domain and a component of a chromatin remodeling complex or its functional fragment;

(2) a polynucleotide (II) encoding (I);

(3) a cell comprising (I) or (II); and

(4) producing (I).

ACTIVITY - Cytostatic; Vasotropic; Antidiabetic; Ophthalmological; Antirheumatic; Antiarthritic; Antipsoriatic; Anti-HIV; Antisickling; Neuroprotective; Nootropic; Cerebroprotective; Antibacterial; Fungicide; Virucide.

No supporting data is given.

MECHANISM OF ACTION - Gene therapy; Modulator of gene expression by modifying gene in cellular chromatin.

No supporting data is given.

USE - (M1) is useful for modifying a region of interest, in particular a gene encoding a product such as vascular endothelial growth factor, erythropoietin, androgen receptor, peroxisome proliferator-activated receptor (PPAR- gamma 2), p16, p53, pRb, dystrophin and e-cadherin in cellular chromatin present in a plant or animal cell, preferably human cell. The chromatin modification facilitates detection of a sequence of interest comprising a single nucleotide polymorphism, activation or repression of a gene of interest or recombination between an exogenous nucleic acid and cellular chromatin. The chromatin modification results in generation of an accessible region in the cellular chromatin which facilitates binding of an exogenous molecule such as polypeptides, nucleic acids, small molecule therapeutics, minor groove binders, major groove binders and intercalators.

(I) may be used for modulating expression of a gene, by contacting cellular domain chromatin with (I) that binds to a binding site in cellular chromatin and further contacting the cellular chromatin with a second molecule that binds to a target site in the gene and modulates expression of the gene. Several first fusion molecules are contacted with cellular chromatin, where each fusion molecule binds to distinct binding site. The first fusion molecule binds to a shared binding site and the second fusion molecule binds to a shared target site in two or more of the several genes. (I) is also useful for binding an exogenous molecule to a binding site located within a gene in cellular chromatin (all claimed).

Targeted remodeling of chromatin facilitates the regulation of many processes involving access of molecules to DNA in cellular chromatin including, replication, recombination, repair, transcription, telomere function and maintenance, sister chromatid cohesion and mitotic chromosome segregation. Targeted modification of chromatin structure is useful in processes such as therapeutic regulation of disease-related genes, engineering of cells for manufacture of protein pharmaceuticals, pharmaceutical discovery (including target discovery, target validation

and engineering of cells for high throughput screening methods) and plant agriculture.

Chromatin modification increases the efficiency of recombination, facilitating targeted integration of an exogenous nucleic acid, modulates expression of human, mammalian, bacterial, fungal, protozoal, archeal, plant and viral genes.

(M1) and (I) also facilitate detection of particular sequences by binding of an exogenous molecule to a binding site in cellular chromatin as in, for example, diagnostic applications, and, in conjunction with methods of binding of exogenous molecules to cellular chromatin, can be used in assays to determine gene function and to determine changes in phenotype resulting from specific modulation of gene expression.

(II) may be used for gene therapy to modulate gene expression, for therapeutic or prophylactic applications, e.g., for treating cancer, ischemia, diabetic retinopathy, macular degeneration, rheumatoid arthritis, psoriasis, HIV infection, sickle cell anemia, Alzheimer's disease, muscular dystrophy, neurodegenerative diseases, vascular disease, cystic fibrosis, stroke and for inhibiting microorganisms, e.g., Chlamydia, Mycobacteria, Pneumococci, infectious fungus, e.g., Candida sp. and viruses, e.g., hepatitis.

Dwg.0/7

FS CPI

FA AB; DCN

MC CPI: B04-E02F; B04-E02H; B04-F0100E; B04-L0400E; B04-N0400E; B04-N08; B11-C08E; B12-K04E; B12-K04F; B14-A02; B14-A02B1; B14-A04A; B14-C09B; B14-F02; B14-F02D; B14-F03; B14-H01; B14-J01; B14-J01A4; B14-J05E; **B14-N03**; B14-N12; B14-N16; B14-N17C; B14-S03A; D05-A02B; D05-H09; D05-H12C; D05-H14; D05-H17C; D05-H18

TECH UPTX: 20020213

TECHNOLOGY FOCUS - BIOTECHNOLOGY - Preparation: (I) is produced by expressing (II) in a suitable host cell (claimed).

Preferred Fusion Polypeptide: The fusion molecule is a fusion polypeptide, where the DNA-binding domain comprises a triplex-forming nucleic acid or a minor groove binder and preferably the domain comprises zinc finger DNA-binding domain. The component of a chromatin remodeling complex or its functional fragment is an enzymatic or non-enzymatic component. The enzymatic component is SWI/SNF complex family member, amphibian cells (Mi-2) complex family member, ISWI complex family member, Brahma (BRM) family member, BRG/BAF complex family member, a Mot-1 complex family member, Chd-1 to Chd-4 family members, histone acetyl transferase and **histone deacetylase.**

Preferred Method: (M1) further comprises contacting a cell with a polynucleotide encoding the fusion polypeptide which is expressed in the cell and identifying an accessible region in the cellular chromatin, where the fusion molecule binds to a target site in the accessible region. The cellular chromatin is further contacted with a second or third molecule, preferably a transcriptional regulatory protein, fusion molecule, fusion polypeptide which comprises a zinc finger DNA-binding domain and a transcriptional activation or repression domain. The second molecule further comprises a polypeptide sequence of a histone acetyl transferase, **histone deacetylase** or their functional fragments.

ABEX UPTX: 20020213

WIDER DISCLOSURE - Methods for constructing (II) are also disclosed.

ADMINISTRATION - Administration is intravenous, intramuscular, intradermal or subcutaneous.

Dosage not specified.

EXAMPLE - A zinc finger DNA-binding domain, which recognizes the human vascular endothelial growth factor-A (VEGF) gene, was designed and constructed according to design rules and methods disclosed in co-owned WO 00/42219, WO 00/41566 and co-owned U.S. Patent Applications Serial No.09/444241 filed November 19, 1999 and 09/535088 filed March 23, 2000. Methyl binding domain proteins (MBDs) participate in repression of the

expression of certain genes by binding to methylated cytosine residues present in CpG dinucleotides and recruiting chromatin remodeling complexes to the site of binding.
DNA N-methyl transferases (DNMTs) methylate cytosine residues present in certain CpG dinucleotide sequences in cellular DNA. Such methylation also leads to chromatin remodeling at or in the vicinity of the methylated sequences.
Repression of VEGF expression by zinc finger protein-(ZFP)-MBD and ZFP-DNMT fusions was studied. A series of ZFP-MBD and ZFP-DNMT fusions were tested for their ability to regulate expression of the human VEGF-A gene.
A series of plasmids was constructed, in which the VEGF3a/1 ZFP binding domain was fused to MBD2b, MBD3, MBD3S, MBD3L, DNMT1, DNMT3a or DNMT3b. The fusion genes also comprised a nuclear localization signal and a FLAG epitope. HeLa cells were transfected with the constructs. Seventy two hours after transfection, secreted VEGF levels were measured using a VEGF enzyme-linked immunosorbent assay (ELISA). Cells were co-transfected with a green fluorescent protein-encoding plasmid to allow measurement of transfection efficiency.
The results showed that transfection of HeLa cells with all of the MBD and DNMT fusions tested resulted in repression of VEGF expression. When corrected for transfection efficiency, intracellular expression of the MBD2b-VEGF3a/1 fusion resulted in 100% repression of VEGF expression. Thus, fusions between a targeted ZFP binding domain and proteins whose mechanism of modulating gene expression involved chromatin remodeling were able to repress gene expression.

L61 ANSWER 26 OF 28 WPIX COPYRIGHT 2004 THOMSON DERWENT on STN
AN 2000-475918 [41] WPIX
CR 2000-482840 [42]; 2001-374953 [39]; 2003-209226 [20]; 2003-247121 [24]; 2003-895308 [82]; 2003-898071 [82]
DNC C2000-142712
TI Method of modulating expression of an endogenous cellular gene in a cell to prevent gene activation or prevent repression of gene expression comprising contacting a target sequence with a zinc finger protein.
DC B04 C06 D16
IN CASE, C C; COX, G N; EISENBERG, S P; JARVIS, E E; SPRATT, S K; COX, I G N
PA (SANA-N) SANAGAMO BIOSCIENCES INC; (SANG-N) SANGAMO BIOSCIENCES INC
CYC 91
PI WO 2000041566 A1 20000720 (200041)* EN 101 A01N063-00 <--
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SL SZ TZ UG ZW
W: AE AL AM AT AU AZ BA BB BG BR BY CA CH CN CR CU CZ DE DK DM EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW
GB 2348424 A 20001004 (200051) C12N015-63 <--
AU 2000028470 A 20000801 (200054) A01N063-00 <--
EP 1061805 A1 20001227 (200102) EN A01N063-00 <--
R: AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE
GB 2348424 B 20010314 (200116) C12N015-63 <--
JP 2001231583 A 20010828 (200157) 50 C12N015-09 <--
AU 745844 B 20020411 (200237) A01N063-00 <--
JP 2002534104 W 20021015 (200282) 165 C12N015-09 <--
US 6534261 B1 20030318 (200322) C12Q001-68
US 2003087817 A1 20030508 (200337) A61K038-48
ADT WO 2000041566 A1 **WO 2000-US409 20000106**; GB 2348424 A **GB 2000-650 20000112**; AU 2000028470 A **AU 2000-28470 20000106**; EP 1061805 A1 **EP 2000-906882 20000106, WO 2000-US409 20000106**; GB 2348424 B **GB 2000-650 20000112**; JP 2001231583 A **Div ex JP 2000-593186 20000106, JP 2001-5820 20000106** ; AU 745844 B **AU 2000-28470 20000106**; JP 2002534104 W **JP 2000-593186 20000106, WO 2000-US409 20000106**; US 6534261 B1

US 1999-229037 19990112; US 2003087817 A1 **Cont of US 1999-229037 19990112, US 2001-897844 20010702**

FDT AU 2000028470 A Based on WO 2000041566; EP 1061805 A1 Based on WO 2000041566; AU 745844 B Previous Publ. AU 2000028470, Based on WO 2000041566; JP 2002534104 W Based on WO 2000041566

PRAI **US 1999-229037 19990112; US 2001-897844 20010702**

IC ICM A01N063-00; A61K038-48; C12N015-09; C12N015-63; C12Q001-68
ICS A61K031-711; A61K035-76; A61K038-16; A61K048-00; A61P007-00; A61P007-06; A61P009-00; A61P009-10; A61P011-00; A61P017-06; A61P019-02; A61P021-00; A61P021-04; A61P025-28; **A61P027-02**; A61P029-00; A61P031-04; A61P031-10; A61P031-12; A61P031-18; A61P035-00; A61P037-00; C07K014-46; C12N005-10; C12N015-12; C12N015-67; C12N015-82; C12N015-85; C12N015-87

AB WO 200041566 A UPAB: 20031223

NOVELTY - Modulating expression of an endogenous cellular gene in a cell comprises contacting a first target site in the endogenous cellular gene with a first zinc finger protein (ZFP).

ACTIVITY - Cytostatic; vasotropic; antidiabetic; antirheumatic; antiarthritic; antipsoriatic; virucide; antianemia; nootropic; neuroprotective; anti-cystic fibrosis; cerebroprotective.

No biological data given.

MECHANISM OF ACTION - Gene therapy.

USE - The method of modulating expression of an endogenous cellular gene in a cell is used to inhibit expression of the gene where the Kd of the ZFP is less than 25 nM and inhibits expression by 20%, preferably 75-100% to prevent gene activation (claimed). The method of modulating expression of an endogenous cellular gene in a cell is also used to activate expression of a developmentally silent or inactive endogenous cellular gene e.g. EPO (undefined), GATA (undefined), hemoglobin gamma, hemoglobin delta, an interleukin, granulocyte macrophage colony stimulating factor (GM-CSF), eutrophin or MyoD (undefined)where the Kd of the ZFP is less than 25 nM and activate expression to at least 150%, preferably 200-500% to prevent repression of gene expression (claimed).

Modulation of gene expression can be used for treating cancer, ischemia, diabetic retinopathy, macular degeneration, rheumatoid arthritis, psoriasis, viral infection, sickle cell anemia, Alzheimer's disease, cystic fibrosis, neurodegenerative diseases and stroke.

ZFPs can be used to engineer plants which have increased disease resistance, modification of flavors, fruit ripening, yield, color, and for enhanced oil production in crop plants.

The ZFPs can also be used in assays to determine the phenotypic consequences and function of gene expression.

The methods can be used to modulate gene expression in transgenic mice.

ADVANTAGE - The modulation methods avoid the need to generate full-length cDNA clones of the gene being studied.

Dwg.0/11

FS CPI

FA AB; DCN

MC CPI: B04-E03B; B04-E03F; B04-E08; B04-F01; B04-N02; B04-P01A0E; B11-C07A; B11-C08E5; B12-K04A3; B12-K04F; B12-M11F; B14-A02; B14-C06; B14-C09B; B14-F02D; B14-F03; B14-H01; B14-J01A4; B14-K01C; B14-N17C; B14-S03; B14-S04; C04-E03B; C04-E03F; C04-E08; C04-F01; C04-N02; C04-P01A0E; C11-C07A; C11-C08E5; C12-K04A3; C12-K04F; C12-M11F; C14-A02; C14-C06; C14-C09B; C14-F02D; C14-F03; C14-H01; C14-J01A4; C14-K01C; C14-N17C; C14-S03; C14-S04; D05-H09; D05-H12A; D05-H12E; D05-H16A; D05-H17A

TECH UPTX: 20000831

TECHNOLOGY FOCUS - BIOTECHNOLOGY - Preferred Method: A delivery vehicle comprising the ZFP is administered to the cell. The delivery vehicle comprises a liposome or a membrane translocation polypeptide. The zinc finger protein is encoded by a nucleic acid operably linked to a promoter and is administered to the cell in a lipid:nucleic acid complex or as

naked nucleic acid or is encoded by an expression vector which is administered to the cell. The expression vector is a viral expression vector e.g. retroviral, adenoviral or an adeno-associated virus (AAV) expression vector. The promoter is an inducible promoter or weak promoter. The level of gene expression regulation by the ZFPs is assessed by in vitro or in vivo assay by measuring e.g. protein or mRNA levels by immunoassay or hybridization assay. Transgenic animals expressing the ZFP or to which the ZFP has been administered by a delivery vehicle can be used to determine expression.
Preferred Protein: The method further comprises contacting a second target site in the endogenous cellular gene with a second ZFP. The first and second sites are adjacent to each other. The first and second ZFPs are covalently linked. The two ZFPs are fusion proteins comprising one and preferably at least two regulatory domains. The regulatory domains are a transcriptional repressor, transcriptional activator, endonuclease, methyl transferase, histone acetyltransferase or a **histone deacetylase**. Expression of ZFP as a fusion protein e.g. a maltose binding protein allows ease of purification and monitoring of expression. The ZFP comprises an SP-1 backbone. The ZFP comprises a regulatory domain and is humanized.
Preferably the ZFP comprises six fingers and a regulatory domain.
Preferred Cell: The cell is an animal, plant, bacterial, protozoal, fungal cell, mammalian or human cell. The cell comprises less than 1.5x106 copies of the ZFP.
Preferred Gene: The endogenous cellular gene is ERalpha, IGF-I (insulin-like growth factor), c/myc, ICAM (undefined), Her2/Neu, FAD2-1 (undefined), EPO (undefined), granulocyte macrophage colony stimulating factor (GM-CSF), GDNF (undefined), LDL-R (undefined) or preferably vascular endothelial growth factor (VEGF). The target site is upstream of or adjacent to a transcription initiation site of the endogenous cellular gene or is adjacent to an RNA polymerase pause site downstream of a transcription initiation site of the endogenous cellular gene.

ABEX UPTX: 20000831

ADMINISTRATION - Gene therapy vectors are administered by systemic or topical application or vectors are delivered to cells ex vivo and then the cells are reimplanted into the patient after selection for cells which have incorporated the vector. Dosage is 1.5x10 power 6 copies of the ZFP per cell.
EXAMPLE - The EPO2C zinc finger protein (ZFP) was designed to recognize a 9 base pair (bp) DNA-binding site located 853 bp upstream of the EPO transcription initiation site. Eukaryotic expression vectors were constructed by fusing the EPO2C ZFP to the SV40 nuclear localization signal (NLS) and the herpes simplex virus (HSV) VP16 transactivation domain. Hep3B cells (a human hepatocellular carcinoma-derived cell line) (2x10 power 6) or HEK293 cells (a human embryonic kidney epithelium derived cell line) were seeded into 6-well plates one day before transfection. The plasmid encoding the ZFP was transiently infected into the cells using Lipofectamin (GIBCO-BRL). Mock transfection and transfection with an empty vector were used as controls. After a day the growth medium was removed and fresh Dulbecco's modified Eagle's medium (DMEM) added. Culture supernatants were collected 24 hours later for determination of EPO protein expression levels using an enzyme linked immunosorbent assay (ELISA) kit. Transfection of a vector encoding the EPO2C ZFP transcativation protein increased the level of EPO expression in both Hep3B and HEK293 cells from less than 2 mU/ml to at least 18 mU/ml when compared to control vector or mock transfected cells.

L61 ANSWER 27 OF 28 WPIX COPYRIGHT 2004 THOMSON DERWENT on STN
AN 2000-317929 [27] WPIX
DNC C2000-096280
TI A cyclic tetrapeptide WF27082, useful as **histone deacetylase** inhibitors, are new..
DC B02 B04 D16

IN HINO, M; MORI, H; SAKAMOTO, K; TAKASE, S; TSURUMI, Y
PA (FUJI) FUJISAWA PHARM CO LTD
CYC 90
PI WO 2000021979 A2 20000420 (200027)* EN 37 C07K005-00 <--
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL
OA PT SD SE SL SZ TZ UG ZW
W: AE AL AM AT AU AZ BA BB BG BR BY CA CH CN CR CU CZ DE DK DM EE ES
FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KR KZ LC LK LR LS LT
LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM
TR TT TZ UA UG US UZ VN YU ZA ZW
AU 9960072 A 20000501 (200036) <--
BR 9914779 A 20010703 (200141) C07K005-00 <--
EP 1123309 A2 20010816 (200147) EN C07K005-12 <--
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT
RO SE SI
CZ 2001001342 A3 20010912 (200158) C07K005-12 <--
KR 2001080142 A 20010822 (200213) C07K005-12 <--
HU 2001003985 A2 20020228 (200223) C07K005-00 <--
CN 1330660 A 20020109 (200229) C07K005-00 <--
MX 2001003742 A1 20010701 (200236) C07K005-00 <--
JP 2002527449 W 20020827 (200271) 49 C07K005-12 <--
ZA 2001003338 A 20021127 (200305) 56 C07K000-00 <--
TW 536544 A 20030611 (200374) C07K005-12
US 6656905 B1 20031202 (200379) A61K038-07
ADT WO 2000021979 A2 **WO 1999-JP5597 19991008**; AU 9960072 A **AU 1999-60072 19991008**; BR 9914779 A **BR 1999-14779 19991008**, **WO 1999-JP5597 19991008**; EP 1123309 A2 **EP 1999-970393 19991008**, **WO 1999-JP5597 19991008**; CZ 2001001342 A3 **WO 1999-JP5597 19991008**, **CZ 2001-1342 19991008**; KR 2001080142 A **KR 2001-704664 20010413**; HU 2001003985 A2 **WO 1999-JP5597 19991008**, **HU 2001-3985 19991008**; CN 1330660 A **CN 1999-814383 19991008**; MX 2001003742 A1 **MX 2001-3742 20010411** ; JP 2002527449 W **WO 1999-JP5597 19991008**, **JP 2000-575884 19991008**; ZA 2001003338 A **ZA 2001-3338 20010424**; TW 536544 A **TW 1999-117518 19991011**; US 6656905 B1 **WO 1999-JP5597 19991008**, **US 2001-806500 20010504**
FDT AU 9960072 A Based on WO 2000021979; BR 9914779 A Based on WO 2000021979; EP 1123309 A2 Based on WO 2000021979; CZ 2001001342 A3 Based on WO 2000021979; HU 2001003985 A2 Based on WO 2000021979; JP 2002527449 W Based on WO 2000021979; US 6656905 B1 Based on WO 2000021979
PRAI **AU 1999-9257 19990316**; **AU 1998-6469 19981013**
IC ICM A61K038-07; C07K000-00; C07K005-00; C07K005-12
ICS A61K038-12; A61K038-55; A61P001-16; A61P003-10; A61P005-48; A61P007-00; A61P029-00; A61P033-00; A61P033-02; A61P035-00; A61P035-02; A61P037-00; A61P037-06; A61P043-00; C07K005-10; C12N001-14; C12N009-99; C12P021-02; C12P021-04; C12R001-645
AB WO 200021979 A UPAB: 20000606
NOVELTY - A cyclic tetrapeptide WF27082 is new.
DETAILED DESCRIPTION - A cyclic tetrapeptide WF27082 (I) is new-
R1 = methyl;
R2 = methyl or ethyl;
R3 = H or methyl; and
R4 = (protected) OH;
With the proviso that when R1 = H, R2 = ethyl.
INDEPENDENT CLAIMS exist for-
(1) A fungal strain belonging to the genus Acremonium, which has a deposit number FERM BP-6539 and which produces a compound having **histone deacetylase** inhibitory activity.
(2) A compound having a **histone deacetylase** inhibitory activity, which is obtained by culturing the genus Acremonium fungal strain FERM BP-6539.
(3) A process for producing WF27082 (I), comprsing the culturing of a

WF27082 producing strain belonging to the genus Acremonium and recovering the compound from the culture broth.

(4) A composition containing (I) for the treatment or prevention of inflammatory disorders, diabetes, diabetic complications, homozygous thalassemia, fibrosis, cirrhosis, acute promyelocytic leukemia (APL), organ transplant rejections, autoimmune diseases, or protozoal infections comprising a compound of formula (I).

(5) A method for treating or preventing inflammatory disorders, diabetes, diabetic complications, homozygous thalassemia, fibrosis, cirrhosis, acute promyelocytic leukemia (APL), organ transplant rejections, autoimmune diseases, or protozoal infections comprising a compound of formula (I).

ACTIVITY - Dermatological; Antipsoriatic; Fungicide; Antiseborrheic; Endocrine-Gen.; Respiratory-Gen.; Antiasthmatic; Antiulcer; Vasotropic; Gastrointestinal-Gen.; Antimigraine; Ophthalmological; Nephrotropic; Antilipemic; Anorectic; CNS-Gen.; Antiparkinsonian; Neuroleptic; Osteopathic; Muscular-Gen.; Nootropic; Antibacterial; Gynecological; Antiarthritic; Anti-HIV; Vulnerary;

The cytotoxic activity of WF27082B against human tumor cell lines was determined in vitro. Concentration of the compound required for 50% inhibition of cell growth (IC50; ng/ml) was examined by plotting the logarithms of the concentration against the growth rate (percentage of control) of the treated cells. Human T cell leukemia Jurkat cells (1 x 105cells /ml) and human colon adenocarcinoma HT-29 cells (5 x 104cells/ml) were treated with WF27082B in 100 mu l of RPMI-1640 medium supplemented with 10% FBS, penicillin (50 units/ml) and streptomycin (50 microns g/ml) in 5% carbon dioxide-95% air atmosphere at 37 deg. C. The cyctotoxicity was colorimetrically determined at 550nm (and 660nm as a reference). WF27082B had IC50 values of 11 ng/ml against human T cell leukemia Jurkat cells and 14 ng/ml against human colon adenocarcinoma HT-29 cells.

MECHANISM OF ACTION - Compounds (I) are **histone deacetylase** inhibitors.

USE - Compounds (I) are useful as a **histone deacetylase** inhibitor for treatment or prevention of inflammatory disorders, diabetes, diabetic complications, homozygous thassalemia, fibrosis, cirrhosis, acute promyelocytic leukemia, organ transplant rejection, autoimmune diseases, protozoal infection or tumors (claimed). Particular conditions treated include, inflammatory or hyperproliferative skin diseases (e.g. psoriasis, dermatitis, lichen planus, erythema, acne, lupus erythematosus or alopecia areata), reversible obstructive airway disease (e.g. asthma or bronchitis), mucosal or vascular inflammation (e.g. ulcers, ischemic or thrombotic vascular injury, ischemic bowel disease or enteritis), intestinal inflammation (e.g. celiac disease, proctitis or Crohn's disease), food associated allergic disorders (e.g. migraine, rhinitis and eczema), eye, renal, respiratory, skin, CNS (e.g. Parkinson's or Alzheimer's disease) or collagen disease, endocrine disorders, hematic disease (e.g. anemia), adiposis, periodontal disease, muscular dystrophy, pyoderma, Down's syndrome, endotoxic shock, restenosis, premature menopause, male sterility, arthritis, HIV, AIDS and keloid. approx.

Dwg.0/0

FS CPI

FA AB; GI; DCN

MC CPI: B04-C01A; B04-F09; B14-A02; B14-C01; B14-C03; B14-D01A; B14-D01B; B14-D07A; B14-E08; B14-F01E; B14-F02D; B14-F03; B14-G01B; B14-G02C; B14-H01; B14-J01A3; B14-J01A4; B14-J05; B14-K01; **B14-N03**; B14-N04; B14-N05; B14-N10; B14-N17; B14-S04; D05-H05

ABEX UPTX: 20000606

ADMINISTRATION - (I) are suitable for external, enteral or parenteral administration, in the form of tablets, pellets, capsules, suppositories, solutions, emulsions,suspensions, injections, ointments, linements, eye drops, lotions, gels and creams.

EXAMPLE - An aqueous seed medium (30ml) containing 4.0% sucrose, 1.0% glucose, 2.0% soluble starch, 3.0% cotton seed flour, 1.5% soybean flour, 1.0% potassium phosphate, 02% calcium carbonate, 0.05% Adekanol LG-109 (defoaming agent, Asaka Denka Co., Ltd) and 0.05% Silicone KM-70 (defoaming agent,Shin-Etsu Chemical Co., Ltd) was poured into a flask and sterilized at 120 degrees C for 30 minutes. A loopful of fungus strain number 27082 was inoculated from a slant culture into the flask and cultured at 25 degrees C for four days. The seed culture was inoculated to 20 l of sterile production medium consisting of 3.0% modified starch, 2.0% cotton seed flour, 0.2% wheat germ, 0.1% potassium phosphate, 0.1% sodium chloride, 0.0005% zinc sulfate heptahydrate, 0.05% Adekanol LG-109 and 0.055 Silicone KM-70 (pH 7.0) in a 30 l jar fermenter. Fermentation was carried out at 25 degrees C for 4 days under aeration at 20 l/min and agitation of 200-300 rpm.

L61 ANSWER 28 OF 28 WPIX COPYRIGHT 2004 THOMSON DERWENT on STN
AN 2000-195552 [17] WPIX
DNC C2000-060749
TI New cyclic tetrapeptide compound useful as inhibitor of **histone deacetylase** for treating organ transplant rejection, autoimmune diseases or tumors.
DC B02
IN ABE, F; HINO, M; MORI, H; TAKASE, S; YOSHIMURA, S
PA (FUJI) FUJISAWA PHARM CO LTD
CYC 24
PI WO 2000008048 A2 20000217 (200017)* EN 21 C07K005-12 <--
RW: AT BE CH CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE
W: BR CA CN JP KR US
ADT WO 2000008048 A2 **WO 1999-JP4148 19990802**
PRAI **AU 1998-5057 19980804**
IC ICM C07K005-12
ICS A61K038-07
AB WO 200008048 A UPAB: 20000405
NOVELTY - **Histone deacetylase** inhibiting cyclic tetrapeptide compound (I) is new.

DETAILED DESCRIPTION - A cyclic tetrapeptide compound of formula (I) (FR225497) is new.

An INDEPENDENT CLAIM is included for the production of (I).

ACTIVITY - Antitumor; immunosuppressant; antiinflammatory; antidiabetic; antiprotozoal; cytostatic; dermatological; ophthalmological; respiratory; neuroprotective; CNS; cardiant; anorectic; muscular; antioxidant; antiviral.

The activity of (I) was determined against (a) human T cell leukemia Jurkat cells and (b) human colon adenocarcinoma HT-29 cells. IC50 values were (a) 152 ng/ml and (b) 158 ng/ml.

MECHANISM OF ACTION - **Histone deacetylase** inhibitor.

In a test to determine the effect of (I) on activity of partially purified human (Jurkat cells) **histone deacetylase**, results for % inhibition were, at 1000 ng/ml 91.7%, at 100 ng/ml 67.5% and at 10 ng/ml 33.4%.

USE - Used for treating or preventing inflammatory disorders, diabetes, diabetic complications, homozygous thalassemia, fibrosis, cirrhosis, acute promyelocytic leukemia, protozoal infection, organ transplant rejection, autoimmune diseases and tumor (all claimed). (I) is also used for treating inflammatory or hyperproliferative skin diseases or cutaneous manifestations of immunologically mediated diseases, autoimmune diseases of the eye, reversible obstructive airways diseases, mucosal or vascular inflammations, intestinal inflammations and allergies, renal diseases, nervous diseases, cerebral ischemic diseases, endocrine diseases, hepatic diseases, bone diseases, respiratory diseases, skin diseases, circulatory diseases, collagen diseases, adiposis, eosinophilic fasciitis, periodontal diseases, nephrotic syndrome, male pattern

alopecia, alopecia senile, muscular dystrophy, pyoderma and Sezary syndrome, chromosome abnormality associated diseases, Addison's disease, active oxygen mediated diseases, intestinal diseases, pulmonary diseases, ocular diseases, HIV infection and AIDS.
Dwg.0/0
FS CPI
FA AB; GI; DCN
MC CPI: B04-C01A; B14-A02B1; B14-A03; B14-C03; B14-D07; B14-E10; B14-E12; B14-F01B; B14-F02D1; B14-G01B; B14-G02; B14-H01; B14-H01A; B14-J01; B14-J05; B14-K01; B14-N01; **B14-N03**; B14-N06B; B14-N10; B14-N12; B14-N17; B14-R02; B14-S04; B14-S08
TECH UPTX: 20000405
TECHNOLOGY FOCUS - ORGANIC CHEMISTRY - Preparation: (I) is obtained from a culture of a Helicoma strain.
ABEX UPTX: 20000405
ADMINISTRATION - The dosage is 0.5 50 mg/kg/day orally or 0.01-10 mg/kg intramuscularly or intravenously. Administration is also topical.

EXAMPLE - An aqueous seed medium (160 ml) containing 1% polypeptone, 2% glucose, 0.3% beef extract, 0.2% yeast extract, 0.1% NaCl (pH 7) was sterilized at 120degreesC for 30 minutes. A slant culture of Helicoma ambiens RF-1023-1 was inoculated in the medium and cultured at 28degreesC on a shaker at 120 rpm for 5-6 days. The seed culture was inoculated to sterile production medium comprising 2% potato starch, 2% sucrose, 0.5% yeast extract, 0.05% AdekanolLG-109 (RTM: defoaming agent) and 0.05% Silicone KM-70, and fermented at 25degreesC for 14 days with aeration and agitation.
The cultured broth (75 l, containing 736 mg (I)) was extracted with 75 l acetone. The acetone extract was filtered and the filtrate diluted and passed through a Diaion HP 20 column, washed and eluted with methanol. The eluate was concentrated to give an oily residue (containing 506 mg (I)). This was dissolved in a small volume of methanol. Column chromatography and extraction with ethyl acetate gave FR225497 (I) (270 mg), m. pt. 193-194degreesC.

=> fil hcaplus
FILE 'HCAPLUS' ENTERED AT 09:57:01 ON 01 SEP 2004

FILE COVERS 1907 - 1 Sep 2004 VOL 141 ISS 10
FILE LAST UPDATED: 31 Aug 2004 (20040831/ED)

This file contains CAS Registry Numbers for easy and accurate substance identification.

=> => d l23 all tot

L23 ANSWER 1 OF 5 HCAPLUS COPYRIGHT 2004 ACS on STN

AN 2004:566563 HCAPLUS
DN 141:123479
ED Entered STN: 15 Jul 2004
TI Preparation of **histone deacetylase** inhibitors N-aryl benzamides for use in pharmaceutical combinations with known angiogenesis inhibitors
IN Schuppan, Detlef; Herold, Christoph; Gansmayer, Marion; Ocker, Matthias; Thierauch, Karl-Heinz
PA Schering Aktiengesellschaft, Germany
SO PCT Int. Appl., 249 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM A61K031-00
CC 25-19 (Benzene, Its Derivatives, and Condensed Benzenoid Compounds)
Section cross-reference(s): 1, 28, 63
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2004058234	A2	20040715	WO 2003-EP14071	20031211

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ

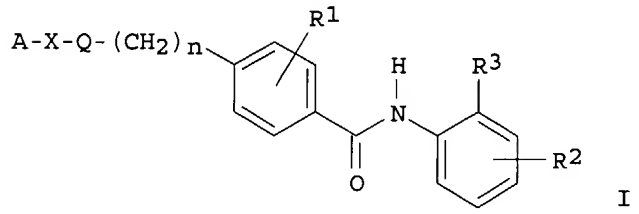
RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRAI EP 2002-90431 A 20021227
EP 2003-90061 A 20030312

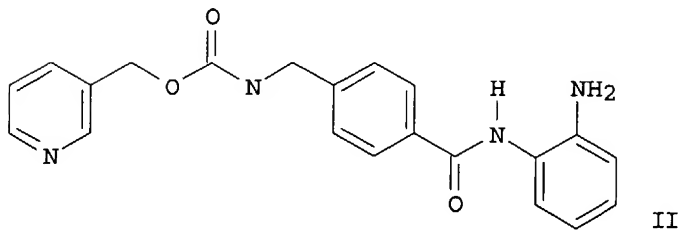
CLASS

PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES
WO 2004058234	ICM	A61K031-00

GI



I



II

AB **Histone deacetylase** inhibitors I [A = (un)substituted

Ph or heterocycle; X = bond, alkyl, alkyloxyalkyl, alkylthioalkyl, etc.; Q = amide, urea, amidoester, etc.; n = 0-4 provided that when X = bond, n is not 0; R1 and R2 independently = H, halo, OH, amino, alkyl, etc.; R3 = OH or amino] and their pharmaceutically acceptable salts are prepared and disclosed as agents to be used in pharmaceutical combinations with phthalazine or pyridazine derivs. (disclosed in prior patent WO 98/35958) which are known angiogenesis inhibitors. Thus, e.g., II was prepared via coupling reaction of 3-pyridinemethanol, N,N'-carbonyldiimidazole and 4-aminomethyl-N-[2-(N-tertbutoxycarbonyl)aminophenyl]benzamide with subsequent removal of N-BOC group. II was combined with tamoxifen and the VEGF receptor antagonist 1-(4-chloroanilino)-4-(pyridylmethyl)phthalazine hydrochloride and this pharmaceutical composition was evaluated in a colorectal carcinoma model in Wag rats. The results of the model study indicated the combination therapy significantly restricted tumor growth relative to the reference (2 ± 0.5% tumor volume) and the individual application of each compound

ST aryl benzamide deriv prepn codrug phthalazine angiogenesis inhibitor; benzamide aryl deriv prepn codrug pyridazine angiogenesis inhibitor; **histone deacetylase** inhibitor aryl benzamide prepn codrug angiogenesis inhibitor

IT Blood vessel, neoplasm
(angiofibroma; preparation of **histone deacetylase** inhibitors N-aryl benzamide derivs. for use in pharmaceutical compns. with known phthalazine or pyridazine angiogenesis inhibitors)

IT Edema
(angioneurotic; preparation of **histone deacetylase** inhibitors N-aryl benzamide derivs. for use in pharmaceutical compns. with known phthalazine or pyridazine angiogenesis inhibitors)

IT Kidney, disease
(diabetic nephropathy; preparation of **histone deacetylase** inhibitors N-aryl benzamide derivs. for use in pharmaceutical compns. with known phthalazine or pyridazine angiogenesis inhibitors)

IT **Eye, disease**
(**diabetic retinopathy**; preparation of **histone deacetylase** inhibitors N-aryl benzamide derivs. for use in pharmaceutical compns. with known phthalazine or pyridazine angiogenesis inhibitors)

IT Kidney, disease
(glomerulonephritis; preparation of **histone deacetylase** inhibitors N-aryl benzamide derivs. for use in pharmaceutical compns. with known phthalazine or pyridazine angiogenesis inhibitors)

IT Kidney, disease
(glomerulus; preparation of **histone deacetylase** inhibitors N-aryl benzamide derivs. for use in pharmaceutical compns. with known phthalazine or pyridazine angiogenesis inhibitors)

IT Blood vessel, neoplasm
(hemangioma; preparation of **histone deacetylase** inhibitors N-aryl benzamide derivs. for use in pharmaceutical compns. with known phthalazine or pyridazine angiogenesis inhibitors)

IT Vascular endothelial growth factor receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(inhibition of; preparation of **histone deacetylase** inhibitors N-aryl benzamide derivs. for use in pharmaceutical compns. with known phthalazine or pyridazine angiogenesis inhibitors)

IT Cell proliferation
(mesangialic cell proliferative disorders; preparation of **histone deacetylase** inhibitors N-aryl benzamide derivs. for use in pharmaceutical compns. with known phthalazine or pyridazine angiogenesis inhibitors)

IT Blood vessel, disease
(microangiopathy, thrombotic; preparation of **histone deacetylase** inhibitors N-aryl benzamide derivs. for use in pharmaceutical compns. with known phthalazine or pyridazine

angiogenesis inhibitors)

IT **Glaucoma (disease)**
(neovascular; preparation of **histone deacetylase** inhibitors N-aryl benzamide derivs. for use in pharmaceutical compns. with known phthalazine or pyridazine angiogenesis inhibitors)

IT Kidney, disease
(nephrosclerosis, malignant; preparation of **histone deacetylase** inhibitors N-aryl benzamide derivs. for use in pharmaceutical compns. with known phthalazine or pyridazine angiogenesis inhibitors)

IT Injury
(nervous tissue; preparation of **histone deacetylase** inhibitors N-aryl benzamide derivs. for use in pharmaceutical compns. with known phthalazine or pyridazine angiogenesis inhibitors)

IT Artery, disease
(occlusion, inhibition of post surgical reocclusion; preparation of **histone deacetylase** inhibitors N-aryl benzamide derivs. for use in pharmaceutical compns. with known phthalazine or pyridazine angiogenesis inhibitors)

IT Angiogenesis
Angiogenesis inhibitors
Antiglaucoma agents
Antitumor agents
Atherosclerosis
Cirrhosis
Drug interactions
Eye, disease
Fibrosis
Human
Kidney, disease
Neoplasm
Transplant rejection
(preparation of **histone deacetylase** inhibitors N-aryl benzamide derivs. for use in pharmaceutical compns. with known phthalazine or pyridazine angiogenesis inhibitors)

IT **9076-57-7, Histone deacetylase**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(inhibitors; preparation of **histone deacetylase** inhibitors N-aryl benzamide derivs. for use in pharmaceutical compns. with known phthalazine or pyridazine angiogenesis inhibitors)

IT 209784-14-5P
RL: PAC (Pharmacological activity); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(preparation of **histone deacetylase** inhibitors N-aryl benzamide derivs. for use in pharmaceutical compns. with known phthalazine or pyridazine angiogenesis inhibitors)

IT

209783-05-1P	209783-09-5P	209783-11-9P	209783-12-0P	209783-14-2P
209783-15-3P	209783-17-5P	209783-19-7P	209783-21-1P	209783-23-3P
209783-25-5P	209783-27-7P	209783-29-9P	209783-31-3P	209783-33-5P
209783-35-7P	209783-37-9P	209783-39-1P	209783-41-5P	209783-43-7P
209783-45-9P	209783-47-1P	209783-49-3P	209783-50-6P	209783-51-7P
209783-55-1P	209783-57-3P	209783-59-5P	209783-61-9P	209783-63-1P
209783-64-2P	209783-65-3P	209783-66-4P	209783-67-5P	209783-68-6P
209783-69-7P	209783-72-2P	209783-73-3P	209783-74-4P	209783-75-5P
209783-76-6P	209783-77-7P	209783-78-8P	209783-79-9P	209783-80-2P
209783-81-3P	209783-82-4P	209783-83-5P	209783-84-6P	209783-85-7P
209783-86-8P	209783-87-9P	209783-88-0P	209783-89-1P	209783-90-4P
209783-91-5P	209783-92-6P	209783-93-7P	209783-95-9P	209783-96-0P
209783-97-1P	209783-98-2P	209783-99-3P	209784-00-9P	209784-01-0P
209784-03-2P	209784-04-3P	209784-05-4P	209784-06-5P	209784-07-6P
209784-09-8P	209784-10-1P	209784-11-2P	209784-12-3P	209784-13-4P
209784-15-6P	209784-16-7P	209784-17-8P	209784-18-9P	209784-20-3P

209784-21-4P 209784-22-5P 209784-23-6P 209784-24-7P 209784-25-8P
209784-27-0P 209784-28-1P 209784-30-5P 209784-31-6P 209784-32-7P
209784-34-9P 209784-35-0P 209784-36-1P 209784-37-2P 209784-38-3P
209784-39-4P 209784-40-7P 209784-41-8P 209784-42-9P 209784-43-0P
209784-44-1P 209784-45-2P 209784-46-3P 209784-49-6P 209784-50-9P
209784-51-0P 209784-52-1P 209784-53-2P 209784-55-4P 209784-56-5P
209784-57-6P 209784-58-7P 209784-59-8P 209784-60-1P 209784-62-3P
209784-64-5P 209784-65-6P 209784-66-7P 209784-67-8P 209784-68-9P
209784-69-0P 209784-70-3P 209784-71-4P 209784-72-5P 209784-73-6P
209784-74-7P 209784-75-8P 209784-76-9P 209784-77-0P 209784-78-1P
209784-79-2P 209784-80-5P 209784-81-6P 241809-88-1P 248925-01-1P
248925-03-3P 248925-07-7P 248925-09-9P 248925-10-2P 722547-65-1P
722547-66-2P 722547-67-3P 722547-68-4P 722547-69-5P 722547-70-8P
722547-71-9P 722547-72-0P 722547-73-1P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of **histone deacetylase** inhibitors N-aryl benzamide derivs. for use in pharmaceutical compns. with known phthalazine or pyridazine angiogenesis inhibitors)

IT 67-98-1, Mer 25 302-22-7 427-51-0, Cyproterone acetate 1100-97-6
1845-11-0, Nafoxidine 1961-77-9 2098-65-9 2098-66-0,
6-Chloro-17-hydroxy-1α,2α-methylenepregna-4,6-diene-3,20-dione
4759-48-2, 13-cis-Retinoic acid 5300-03-8, 9-cis-Retinoic acid
10540-29-1, Tamoxifen 13311-84-7, Flutamide 15262-77-8 15386-27-3
17172-36-0 52806-53-8 63094-42-8 64378-69-4 67392-87-4,
Dihydrospirorenone 73528-58-2 84371-65-3 84449-90-1 91175-91-6
92009-03-5 93678-15-0 96346-61-1, Onapristone 98007-99-9
119840-26-5 189188-64-5 212141-52-1 212141-54-3 212141-57-6
212141-58-7 212141-59-8 212141-60-1 212141-64-5 212141-66-7
212141-67-8 212141-68-9 212141-69-0 212141-70-3 212141-72-5
212141-73-6 212141-74-7 212141-75-8 212141-88-3 212141-91-8
212141-92-9 212142-18-2 212142-81-9 212142-82-0 722547-82-2
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(preparation of **histone deacetylase** inhibitors N-aryl benzamide derivs. for use in pharmaceutical compns. with known phthalazine or pyridazine angiogenesis inhibitors)

IT 56-91-7, 4-Aminomethylbenzoic acid 88-74-4, 2-Nitroaniline 95-54-5,
o-Phenylenediamine, reactions 98-88-4, Benzoylchloride 100-46-9,
Benzylamine, reactions 100-55-0, 3-Pyridinemethanol 103-80-0,
Phenylacetyl chloride 109-00-2, 3-Hydroxypyridine 120-93-4, Ethylene
urea 122-04-3, 4-Nitrobenzoyl chloride 122-60-1 619-66-9,
Terephthalaldehydic acid 1099-45-2 1679-64-7, Monomethyl terephthalate
1798-11-4, 4-Nitrophenoxyacetic acid 2417-72-3, Methyl
4-bromomethylbenzoate 2892-62-8 3731-52-0, 3-Picolylamine 5292-43-3,
tert-Butyl bromoacetate 6419-36-9, 3-Pyridineacetic acid, hydrochloride
6908-41-4, Methyl 4-hydroxymethylbenzoate 6959-48-4 39149-80-9,
tert-Butyl 2-bromopropionate 53117-17-2 209785-29-5
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of **histone deacetylase** inhibitors N-aryl benzamide derivs. for use in pharmaceutical compns. with known phthalazine or pyridazine angiogenesis inhibitors)

IT 130029-61-7P 146651-75-4P 166739-14-6P 209784-84-9P 209784-85-0P
209784-86-1P 209784-87-2P 209784-88-3P 209784-90-7P 209784-91-8P
209784-93-0P 209784-94-1P 209784-95-2P 209784-96-3P 209784-97-4P
209785-01-3P 209785-02-4P 209785-04-6P 209785-05-7P 209785-06-8P
209785-07-9P 209785-08-0P 209785-09-1P 209785-12-6P 209785-15-9P
209785-16-0P 209785-17-1P 209785-18-2P 209785-19-3P 209785-20-6P
209785-21-7P 209785-22-8P 209785-23-9P 209785-24-0P 209785-25-1P
209785-26-2P 209785-27-3P 209785-28-4P 313659-32-4P 431896-87-6P
722547-74-2P 722547-76-4P 722547-77-5P 722547-78-6P 722547-79-7P
722547-80-0P 722547-81-1P

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of **histone deacetylase** inhibitors N-aryl benzamide derivs. for use in pharmaceutical compns. with known phthalazine or pyridazine angiogenesis inhibitors)

L23 ANSWER 2 OF 5 HCAPLUS COPYRIGHT 2004 ACS on STN
AN 2004:392325 HCAPLUS
DN 140:386067
ED Entered STN: 14 May 2004
TI **Histone deacetylase** (HDAC) inhibitors for the treatment of ocular neovascular or edematous disorders and diseases
IN Klimko, Peter G.; Bingaman, David P.
PA Alcon, Inc., Switz.
SO U.S. Pat. Appl. Publ., 8 pp.
CODEN: USXXCO
DT Patent
LA English
IC ICM A61K031-44
ICS A61K031-40; A61K031-19
NCL 514357000; 514408000; 514575000
CC 1-12 (Pharmacology)
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI US 2004092558	A1	20040513	US 2003-697135	20031030
WO 2004043352	A2	20040527	WO 2003-US34617	20031030
WO 2004043352	A3	20040715		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR

PRAI US 2002-425574P P 20021112

CLASS

PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES
US 2004092558	ICM	A61K031-44
	ICS	A61K031-40; A61K031-19
	NCL	514357000; 514408000; 514575000

OS MARPAT 140:386067
AB The invention discloses ophthalmic compns. containing HDAC inhibitors and their use for treating ocular neovascular or edematous diseases and disorders.
ST **histone deacetylase** inhibitor eye neovascular edematous disease treatment
IT **Eye, disease**
(Fuch's heterochromic **iridocyclitis**; **histone deacetylase** inhibitors for treatment of ocular neovascular or edematous diseases)
IT Drug delivery systems
(capsules; **histone deacetylase** inhibitors for treatment of ocular neovascular or edematous diseases)
IT Ischemia
(carotid artery; **histone deacetylase** inhibitors for treatment of ocular neovascular or edematous diseases)
IT Artery
(carotid, ischemia; **histone deacetylase** inhibitors for treatment of ocular neovascular or edematous diseases)
IT **Eye**

(choroid, choroidal thrombosis; **histone deacetylase** inhibitors for treatment of ocular neovascular or edematous diseases)

IT **Eye**
(choroid, choroidal vascular insufficiency; **histone deacetylase** inhibitors for treatment of ocular neovascular or edematous diseases)

IT **Eye, disease**
(contusive ocular **injury**; **histone deacetylase** inhibitors for treatment of ocular neovascular or edematous diseases)

IT **Eye**
(cornea, corneal angiogenesis; **histone deacetylase** inhibitors for treatment of ocular neovascular or edematous diseases)

IT **Eye**
(cornea, corneal **neovascularization**; **histone deacetylase** inhibitors for treatment of ocular neovascular or edematous diseases)

IT **Eye, disease**
(**diabetic retinopathy**; **histone deacetylase** inhibitors for treatment of ocular neovascular or edematous diseases)

IT Anti-ischemic agents
Antiglaucoma agents
Antitumor agents
Cardiovascular agents
Eye, disease
Glaucoma (disease)
Neoplasm
(**histone deacetylase** inhibitors for treatment of ocular neovascular or edematous diseases)

IT **Eye, disease**
(**iritis**, rubeosis **iritis**; **histone deacetylase** inhibitors for treatment of ocular neovascular or edematous diseases)

IT **Eye, disease**
(**macula, senile degeneration**; **histone deacetylase** inhibitors for treatment of ocular neovascular or edematous diseases)

IT Angiogenesis
(neovascularization, eye, neovascularization resulting from combined vitrectomy and lensectomy; **histone deacetylase** inhibitors for treatment of ocular neovascular or edematous diseases)

IT Angiogenesis
(neovascularization, eye; **histone deacetylase** inhibitors for treatment of ocular neovascular or edematous diseases)

IT **Eye, disease**
(**neovascularization, neovascularization** resulting from combined vitrectomy and lensectomy; **histone deacetylase** inhibitors for treatment of ocular neovascular or edematous diseases)

IT **Eye, disease**
(**neovascularization**; **histone deacetylase** inhibitors for treatment of ocular neovascular or edematous diseases)

IT Vein, disease
(occlusion, retinal vein; **histone deacetylase** inhibitors for treatment of ocular neovascular or edematous diseases)

IT Drug delivery systems
(ophthalmic; **histone deacetylase** inhibitors for treatment of ocular neovascular or edematous diseases)

IT **Eye, disease**
(**periretinal proliferation**; **histone deacetylase** inhibitors for treatment of ocular neovascular or edematous diseases)

IT **Eye, disease**
(**retina, detachment; histone deacetylase** inhibitors for treatment of ocular neovascular or edematous diseases)
IT **Eye, disease**
(**retina, ischemia; histone deacetylase** inhibitors for treatment of ocular neovascular or edematous diseases)
IT **Eye, disease**
(**retinopathy**, microvasculopathy; **histone deacetylase** inhibitors for treatment of ocular neovascular or edematous diseases)
IT **Eye, disease**
(**retinopathy**, retinal (macular) edema; **histone deacetylase** inhibitors for treatment of ocular neovascular or edematous diseases)
IT **Eye, disease**
(**retinopathy**, sickle cell **retinopathy**; **histone deacetylase** inhibitors for treatment of ocular neovascular or edematous diseases)
IT **Eye, disease**
(**retrolental fibroplasia; histone deacetylase** inhibitors for treatment of ocular neovascular or edematous diseases)
IT Drug delivery systems
(solns., i.v.; **histone deacetylase** inhibitors for treatment of ocular neovascular or edematous diseases)
IT **Eye, disease**
(**uveitis; histone deacetylase** inhibitors for treatment of ocular neovascular or edematous diseases)
IT **9076-57-7, Histone deacetylase**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(**histone deacetylase** inhibitors for treatment of ocular neovascular or edematous diseases)
IT 149647-78-9 151720-43-3 209783-80-2 251456-60-7 287383-59-9
329966-97-4 329967-02-4 382180-17-8 674767-32-9
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**histone deacetylase** inhibitors for treatment of ocular neovascular or edematous diseases)

L23 ANSWER 3 OF 5 HCAPLUS COPYRIGHT 2004 ACS on STN
AN 2004:392299 HCAPLUS
DN 140:395534
ED Entered STN: 14 May 2004
TI **Histone deacetylase** inhibitors for treating degenerative diseases of the eye
IN **Hellberg, Peggy E.**
PA USA
SO U.S. Pat. Appl. Publ., 5 pp.
CODEN: USXXCO
DT Patent
LA English
IC ICM A61K031-00
ICS A61K038-00
NCL 514002000; 514001000
CC 63-6 (Pharmaceuticals)
Section cross-reference(s): 1
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE	
PI	US 2004092431	A1	20040513	US 2003-694309	20031027	<--
	WO 2004043348	A2	20040527	WO 2003-US33873	20031027	<--

WO 2004043348 A3 20040715
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR
PRAI US 2002-425576P P 20021112 <--
CLASS

PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES
US 2004092431	ICM	A61K031-00
	ICS	A61K038-00
	NCL	514002000; 514001000

AB Compns. and methods for treating degenerative conditions and diseases of the eye with **histone deacetylase** inhibitors are disclosed.
ST eye disease **histone deacetylase** inhibitor
IT **Eye, disease**
(degenerative; **histone deacetylase** inhibitors for treating degenerative diseases of the eye)
IT Peptides, biological studies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(depsipeptides; **histone deacetylase** inhibitors for treating degenerative diseases of the eye)
IT **Glaucoma (disease)**
Human
(**histone deacetylase** inhibitors for treating degenerative diseases of the eye)
IT **Eye, disease**
(**retinopathy; histone deacetylase** inhibitors for treating degenerative diseases of the eye)
IT 38937-66-5 58880-19-6, Trichostatin a 149647-78-9, Suberoylanilide hydroxamic acid 151720-43-3, Oxamflatin 209783-80-2, Ms275
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**histone deacetylase** inhibitors for treating degenerative diseases of the eye)
IT **9076-57-7, Histone deacetylase**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(inhibitors; **histone deacetylase** inhibitors for treating degenerative diseases of the eye)

L23 ANSWER 4 OF 5 HCAPLUS COPYRIGHT 2004 ACS on STN
AN 2004:120847 HCAPLUS
DN 140:163701
ED Entered STN: 13 Feb 2004
TI Preparation of substituted thiophene-2-hydroxamic acids as **histone deacetylase** inhibitors useful against disorders involving increased cell proliferation
IN Archer, Janet Ann; Bordogna, Walter; Bull, Richard James; Clark, David Edward; Dyke, Hazel Joan; Gill, Matthew Iain Andrew; Harris, Neil Victor; Van Den Heuvel, Marco; Price, Stephen
PA Argenta Discovery Limited, UK
SO PCT Int. Appl., 218 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM C07D409-04
ICS C07D413-04; C07D409-14; C07D417-14; C07D413-14; A61K031-38; A61P035-00
CC 27-8 (Heterocyclic Compounds (One Hetero Atom))

Section cross-reference(s): 1

FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2004013130	A1	20040212	WO 2003-GB3168	20030724

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRAI GB 2002-18040 A 20020802

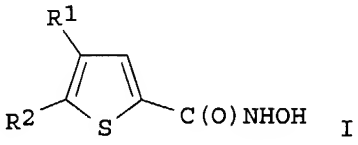
GB 2003-10462 A 20030507

CLASS

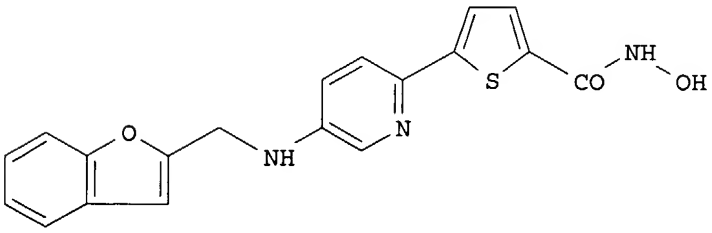
PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES
WO 2004013130	ICM	C07D409-04
	ICS	C07D413-04; C07D409-14; C07D417-14; C07D413-14; A61K031-38; A61P035-00

OS MARPAT 140:163701

GI



I



II

AB Thiophene-2-hydroxamic acids (shown as I; variables defined below; e.g. II) and corresponding N-oxides, pharmaceutically acceptable salts, solvates and prodrugs of such compds. and their use in the treatment of diseases associated with **histone deacetylase** enzymic activity (e.g. cancer, psoriasis, fibroproliferative disorders, smooth muscle cell proliferation disorders, etc.) are claimed. Although the methods of preparation are not claimed, >100 example prepns. are included. For example, 5-(2-methyl-5-trifluoromethyl-2H-pyrazol-3-yl)thiophene-2-carboxylic acid hydroxyamide was prepared in 96% yield deprotection of 5-(2-methyl-5-trifluoromethyl-2H-pyrazol-3-yl)thiophene-2-carboxylic acid (tetrahydropyran-2-yloxy)amide in MeOH using p-toluenesulfonic acid; the reactant was prepared in 78% yield by amide formation of 5-[2-methyl-5-(trifluoromethyl)-2H-pyrazol-3-yl]thiophene-2-carboxylic acid with O-(tetrahydro-2H-pyran-2-yl)hydroxylamine in DMF using diisopropylethylamine and O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate. **Histone**

deacetylase inhibitory activity is reported for 6 examples of I, e.g. IC50 0.062 μM for II; 5 of these were tested for their ability to reduce cell proliferation in 2 cell lines (MCF-7 and MDA-MB-231; human mammary gland adenocarcinoma), e.g. IC50 = 0.6 and 2.0 μM, resp. for II. For I: R1 = aryl or heteroaryl, each (un)substituted by ≥1 R3, alkylenedioxy, carboxy, cyano, halo, hydroxy, nitro, haloalkyl, haloalkoxy, -C(O)R3, -C(O)OR3, -C(:Z)NR4R5, -NR4R5, -NR6C(O)OR3, -NR6C(O)NR4R5, -NR6C(:Z)R3, -OC(O)NR4R5, -NR6SO2R3, -OR3, -OC(O)R3, -SH, -SR3, -SOR3, -SO2R3 and -SO2NR4R5; R2 = H, chloro, cyano, fluoro, alkoxy, alkyl, or haloalkyl; R3 = aryl, heteroaryl, cycloalkyl, cycloalkenyl, heterocycloalkyl or R7; R4 and R5 = H, alkyl, alkenyl, aryl, heteroaryl, cycloalkyl, cycloalkenyl or heterocycloalkyl, wherein said alkyl or alkenyl are (un)substituted by aryl, heteroaryl, cycloalkyl, cycloalkenyl or heterocycloalkyl; or the group -NR4R5 may form a cyclic amine; R6 = H or lower alkyl; R7 = alkyl, alkenyl and alkynyl, wherein said alkyl, alkenyl or alkynyl are (un)substituted by ≥1 aryl, heteroaryl, cycloalkyl, cycloalkenyl, heterocycloalkyl, hydroxy, -C(:Z)NR4R5, -NR4R5, -NR6C(:Z)R8, -OC(O)NR4R5, -NR6C(O)OR8, -NR6C(O)NR4R5, -NR6SO2R8, -OR8, -SOR8, SO2R8 and -SO2NR4R5; R8 = alkyl, alkenyl or alkynyl, (un)substituted by ≥1 aryl, heteroaryl, cycloalkyl, cycloalkenyl, heterocycloalkyl, hydroxy and halogen; or R8 = aryl, heteroaryl, cycloalkyl, cycloalkenyl or heterocycloalkyl; and Z is O or S.

ST thiophene hydroxamic acid **histone deacetylase** inhibitor antiproliferative

IT Nervous system, disease
(Huntington's chorea; preparation of substituted thiophene-2-hydroxamic acids as **histone deacetylase** inhibitors useful against disorders involving increased cell proliferation)

IT Nervous system, disease
(degeneration; preparation of substituted thiophene-2-hydroxamic acids as **histone deacetylase** inhibitors useful against disorders involving increased cell proliferation)

IT Nervous system agents
(degenerative; preparation of substituted thiophene-2-hydroxamic acids as **histone deacetylase** inhibitors useful against disorders involving increased cell proliferation)

IT **Eye, disease**
(**diabetic retinopathy**; preparation of substituted thiophene-2-hydroxamic acids as **histone deacetylase** inhibitors useful against disorders involving increased cell proliferation)

IT Cell proliferation
(diseases caused by increased cell proliferation; preparation of substituted thiophene-2-hydroxamic acids as **histone deacetylase** inhibitors useful against disorders involving increased cell proliferation)

IT Angiogenesis
(diseases involving; preparation of substituted thiophene-2-hydroxamic acids as **histone deacetylase** inhibitors useful against disorders involving increased cell proliferation)

IT Hematopoiesis
(disorders; preparation of substituted thiophene-2-hydroxamic acids as **histone deacetylase** inhibitors useful against disorders involving increased cell proliferation)

IT Hydroxamic acids
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(drug candidates; preparation of thiophene-2-hydroxamic acids as **histone deacetylase** inhibitors useful against disorders involving increased cell proliferation)

IT Heart, disease
(failure; preparation of substituted thiophene-2-hydroxamic acids as

histone deacetylase inhibitors useful against disorders involving increased cell proliferation)

IT Fibrosis
(fibroproliferative disorders; preparation of substituted thiophene-2-hydroxamic acids as **histone deacetylase** inhibitors useful against disorders involving increased cell proliferation)

IT Liver, disease
(fibrosis; preparation of substituted thiophene-2-hydroxamic acids as **histone deacetylase** inhibitors useful against disorders involving increased cell proliferation)

IT Diabetes mellitus
(insulin-dependent; preparation of substituted thiophene-2-hydroxamic acids as **histone deacetylase** inhibitors useful against disorders involving increased cell proliferation)

IT **Eye, disease**
(**keratitis**, interstitial; preparation of substituted thiophene-2-hydroxamic acids as **histone deacetylase** inhibitors useful against disorders involving increased cell proliferation)

IT **Eye, disease**
(**macula**, **senile degeneration**; preparation of substituted thiophene-2-hydroxamic acids as **histone deacetylase** inhibitors useful against disorders involving increased cell proliferation)

IT Heart
(myocyte, congestive heart failure due to cardiomycyte hypertrophy; preparation of substituted thiophene-2-hydroxamic acids as **histone deacetylase** inhibitors useful against disorders involving increased cell proliferation)

IT Allergy
Allergy inhibitors
Anemia (disease)
Angiogenesis inhibitors
Anti-inflammatory agents
Antiarteriosclerotics
Antidiabetic agents
Antimalarials
Antirheumatic agents
Antitumor agents
Arteriosclerosis
Cardiovascular agents
Coccidiosis
Coccidiostats
Cytotoxic agents
Fungicides
Human
Immunomodulators
Lupus erythematosus
Malaria
Mycosis
Neoplasm
Parasiticides
Protozoacides
Psoriasis
Rheumatoid arthritis
Sickle cell anemia
Thalassemia
(preparation of substituted thiophene-2-hydroxamic acids as **histone deacetylase** inhibitors useful against disorders involving increased cell proliferation)

IT Infection
(protozoal; preparation of substituted thiophene-2-hydroxamic acids as

histone deacetylase inhibitors useful against disorders involving increased cell proliferation)

IT Artery, disease
(restenosis; preparation of substituted thiophene-2-hydroxamic acids as **histone deacetylase** inhibitors useful against disorders involving increased cell proliferation)

IT **Eye, disease**
(**retinopathy**; preparation of substituted thiophene-2-hydroxamic acids as **histone deacetylase** inhibitors useful against disorders involving increased cell proliferation)

IT Antiglaucoma agents
Glaucoma (disease)
(rubeotic; preparation of substituted thiophene-2-hydroxamic acids as **histone deacetylase** inhibitors useful against disorders involving increased cell proliferation)

IT Muscle, disease
(smooth, cell proliferation disorders; preparation of substituted thiophene-2-hydroxamic acids as **histone deacetylase** inhibitors useful against disorders involving increased cell proliferation)

IT Toxoplasma gondii
(toxoplasmosis from; preparation of substituted thiophene-2-hydroxamic acids as **histone deacetylase** inhibitors useful against disorders involving increased cell proliferation)

IT Inflammation
(treatable by immune modulation; preparation of substituted thiophene-2-hydroxamic acids as **histone deacetylase** inhibitors useful against disorders involving increased cell proliferation)

IT 656224-95-2P, 4-Methyl-5-(5-trifluoromethyl-1H-pyrazol-3-yl)thiophene-2-carboxylic acid hydroxyamide 656224-98-5P, 4-Methyl-5-(5-trifluoromethyl-1H-pyrazol-3-yl)thiophene-2-carboxylic acid (tetrahydropyran-2-yloxy)amide 656225-00-2P, 5-(5-Phenethylaminopyridin-2-yl)thiophene-2-carboxylic acid hydroxyamide
RL: PAC (Pharmacological activity); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(drug candidate; preparation of thiophene-2-hydroxamic acids as **histone deacetylase** inhibitors useful against disorders involving increased cell proliferation)

IT 656224-27-0P, 5-(2-Methyl-5-trifluoromethyl-2H-pyrazol-3-yl)thiophene-2-carboxylic acid hydroxyamide 656224-29-2P, 5-(2-Methyl-2H-pyrazol-3-yl)thiophene-2-carboxylic acid hydroxyamide 656224-32-7P, 5-(1-Methyl-1H-pyrazol-3-yl)thiophene-2-carboxylic acid hydroxyamide 656224-33-8P, 5-(5-Trifluoromethyl-1H-pyrazol-3-yl)thiophene-2-carboxylic acid hydroxyamide 656224-35-0P, 5-(1-Methyl-5-trifluoromethyl-1H-pyrazol-3-yl)thiophene-2-carboxylic acid hydroxyamide 656224-37-2P, 5-(5-Trifluoromethylisoxazol-3-yl)thiophene-2-carboxylic acid hydroxyamide 656224-39-4P, 5-Phenylthiophene-2-carboxylic acid hydroxyamide 656224-41-8P, 5-(Pyridin-2-yl)thiophene-2-carboxylic acid hydroxyamide 656224-43-0P, [2,2']Bithiophenyl-5-carboxylic acid hydroxyamide 656224-45-2P, 5-(4-Methoxyphenyl)thiophene-2-carboxylic acid hydroxyamide 656224-47-4P, 5-(2H-Pyrazol-3-yl)thiophene-2-carboxylic acid hydroxyamide 656224-49-6P, 5-(1-Benzyl-1H-pyrazol-3-yl)thiophene-2-carboxylic acid hydroxyamide 656224-51-0P, 5-(1-Phenethyl-1H-pyrazol-3-yl)thiophene-2-carboxylic acid hydroxyamide 656224-53-2P, 5-(4-Trifluoromethyl-1H-imidazol-2-yl)thiophene-2-carboxylic acid hydroxyamide 656224-55-4P, 5-(3-Methyl-[1,2,4]oxadiazol-5-yl)thiophene-2-carboxylic acid hydroxyamide 656224-57-6P, 5-[1-[2-(Benzyloxy)ethyl]-1H-pyrazol-3-yl]thiophene-2-carboxylic acid hydroxyamide 656224-59-8P, 5-[1-(3-Phenylpropyl)-1H-pyrazol-3-yl]thiophene-2-carboxylic acid hydroxyamide 656224-61-2P, 5-[1-[(2,3-Dihydrobenzo[1,4]dioxin-2-yl)methyl]-1H-pyrazol-3-yl]thiophene-2-carboxylic acid hydroxyamide 656224-63-4P, 5-[1-[2-(4-

Trifluoromethylphenyl)ethyl]-1H-pyrazol-3-yl]thiophene-2-carboxylic acid hydroxyamide 656224-65-6P, 5-[1-[(Benzo[1,3]dioxol-5-yl)methyl]-1H-pyrazol-3-yl]thiophene-2-carboxylic acid hydroxyamide 656224-67-8P, 5-[1-[2-(4-Trifluoromethoxyphenyl)ethyl]-1H-pyrazol-3-yl]thiophene-2-carboxylic acid hydroxyamide 656224-69-0P, 5-[1-[2-(4-Fluorophenyl)ethyl]-1H-pyrazol-3-yl]thiophene-2-carboxylic acid hydroxyamide 656224-71-4P, 5-[1-(1-Phenylethyl)-1H-pyrazol-3-yl]thiophene-2-carboxylic acid hydroxyamide 656224-73-6P, 5-[1-[2-(Morpholin-4-yl)ethyl]-1H-pyrazol-3-yl]thiophene-2-carboxylic acid hydroxyamide 656224-75-8P, 5-[1-(Tetrahydropyran-2-ylmethyl)-1H-pyrazol-3-yl]thiophene-2-carboxylic acid hydroxyamide 656224-77-0P, 5-[4-(Benzyloxy)pyrimidin-2-yl]thiophene-2-carboxylic acid hydroxyamide 656224-79-2P, 5-(5-Phenethyl-1H-pyrazol-3-yl)thiophene-2-carboxylic acid hydroxyamide 656224-81-6P, 5-(2-Phenethyl-1H-imidazol-4-yl)thiophene-2-carboxylic acid hydroxyamide 656224-83-8P, 5-(Pyrimidin-2-yl)thiophene-2-carboxylic acid hydroxyamide 656224-85-0P, 5-(1-Phenethyl-5-trifluoromethyl-1H-pyrazol-3-yl)thiophene-2-carboxylic acid hydroxyamide 656224-87-2P, 5-(Pyridin-3-yl)thiophene-2-carboxylic acid hydroxyamide 656224-89-4P, 5-(Pyridin-4-yl)thiophene-2-carboxylic acid hydroxyamide 656224-91-8P, 5-(5-Trifluoromethyl-1H-[1,2,4]triazol-3-yl)thiophene-2-carboxylic acid hydroxyamide 656224-93-0P, 5-[5-(3-Phenylpropionylamino)pyridin-2-yl]thiophene-2-carboxylic acid hydroxyamide 656224-96-3P, 5-[3-(Benzyloxy)phenyl]thiophene-2-carboxylic acid hydroxyamide 656225-01-3P, 5-(1-Pent-4-ynyl-1H-pyrazol-3-yl)thiophene-2-carboxylic acid hydroxyamide 656225-03-5P, 5-[1-(3-Phenylallyl)-1H-pyrazol-3-yl]thiophene-2-carboxylic acid hydroxyamide 656225-05-7P, 5-[1-(3-Phenoxypropyl)-1H-pyrazol-3-yl]thiophene-2-carboxylic acid hydroxyamide 656225-07-9P, 5-[1-[2-(Benzoylamino)ethyl]-1H-pyrazol-3-yl]thiophene-2-carboxylic acid hydroxyamide 656225-09-1P, 5-[1-[(Pyridin-4-yl)methyl]-1H-pyrazol-3-yl]thiophene-2-carboxylic acid hydroxyamide 656225-11-5P, 5-[1-[(5-tert-Butyl-[1,2,4]oxadiazol-3-yl)methyl]-1H-pyrazol-3-yl]thiophene-2-carboxylic acid hydroxyamide 656225-14-8P, 5-[1-[3-(Pyrrol-1-yl)propyl]-1H-pyrazol-3-yl]thiophene-2-carboxylic acid hydroxyamide 656225-16-0P, 5-(1-But-2-enyl-1H-pyrazol-3-yl)thiophene-2-carboxylic acid hydroxyamide 656225-18-2P, 5-[5-(2-Phenoxyacetylamino)pyridin-2-yl]thiophene-2-carboxylic acid hydroxyamide 656225-20-6P, 5-[5-[(Phenylacetyl)amino]pyridin-2-yl]thiophene-2-carboxylic acid hydroxyamide 656225-22-8P, 5-[1-[(Quinolin-2-yl)methyl]-1H-pyrazol-3-yl]thiophene-2-carboxylic acid hydroxyamide 656225-24-0P, 5-[5-(Benzoylamino)pyridin-2-yl]thiophene-2-carboxylic acid hydroxyamide 656225-26-2P, N-[6-[5-(Hydroxycarbamoyl)thiophen-2-yl]pyridin-3-yl]isonicotinamide 656225-28-4P, 5-[5-[(Quinolin-2-ylmethyl)amino]pyridin-2-yl]thiophene-2-carboxylic acid hydroxyamide 656225-30-8P, 5-[5-[[(2,3-Dihydrobenzo[1,4]dioxin-6-yl)methyl]amino]pyridin-2-yl]thiophene-2-carboxylic acid hydroxyamide 656225-32-0P, 5-[5-[(Benzofuran-2-ylmethyl)amino]pyridin-2-yl]thiophene-2-carboxylic acid hydroxyamide 656225-34-2P, 5-[1-[2-(4-Fluorobenzyloxy)ethyl]-1H-pyrazol-3-yl]thiophene-2-carboxylic acid hydroxyamide 656225-36-4P, 5-[1-[(Phenylcarbamoyl)methyl]-1H-pyrazol-3-yl]thiophene-2-carboxylic acid hydroxyamide 656225-38-6P, 5-[1-[[(Pyridin-2-ylmethyl)carbamoyl]methyl]-1H-pyrazol-3-yl]thiophene-2-carboxylic acid hydroxyamide 656225-40-0P, 5-[1-[(Quinolin-8-ylcarbamoyl)methyl]-1H-pyrazol-3-yl]thiophene-2-carboxylic acid hydroxyamide 656225-42-2P, 5-[1-[[(5-Trifluoromethyl-[1,3,4]thiadiazol-2-yl)carbamoyl]methyl]-1H-pyrazol-3-yl]thiophene-2-carboxylic acid hydroxyamide 656225-44-4P, 5-[1-[(2-Methoxyphenylcarbamoyl)methyl]-1H-pyrazol-3-yl]thiophene-2-carboxylic acid hydroxyamide 656225-46-6P, 5-[1-[(4-Fluorophenylcarbamoyl)methyl]-1H-pyrazol-3-yl]thiophene-2-carboxylic acid hydroxyamide 656225-48-8P, 5-[1-[(3-Fluorophenylcarbamoyl)methyl]-1H-pyrazol-3-yl]thiophene-2-carboxylic acid hydroxyamide 656225-50-2P, Quinoline-2-carboxylic acid [2-[3-(5-hydroxycarbamoylthiophen-2-yl)pyrazol-1-yl]ethyl]amide 656225-52-4P, 5-[1-[(Benzylcarbamoyl)methyl]-1H-pyrazol-3-yl]thiophene-2-

carboxylic acid hydroxyamide 656225-54-6P, 5-[1-[(N-Ethyl-N-phenylcarbamoyl)methyl]-1H-pyrazol-3-yl]thiophene-2-carboxylic acid hydroxyamide 656225-56-8P, 5-[1-[2-(1H-Indol-3-yl)ethyl]-1H-pyrazol-3-yl]thiophene-2-carboxylic acid hydroxyamide 656225-58-0P, 5-[1-[(2-Trifluoromethoxyphenylcarbamoyl)methyl]-1H-pyrazol-3-yl]thiophene-2-carboxylic acid hydroxyamide 656225-60-4P, 5-[1-[3-(4-Chlorophenyl)propyl]-1H-pyrazol-3-yl]thiophene-2-carboxylic acid hydroxyamide 656225-62-6P, 5-[1-[[[2-(1H-Indol-3-yl)ethyl]carbamoyl]methyl]-1H-pyrazol-3-yl]thiophene-2-carboxylic acid hydroxyamide 656225-64-8P, 5-[1-[(Phenethylcarbamoyl)methyl]-1H-pyrazol-3-yl]thiophene-2-carboxylic acid hydroxyamide 656225-66-0P, 5-[1-[(Isoquinolin-1-yl)methyl]-1H-pyrazol-3-yl]thiophene-2-carboxylic acid hydroxyamide 656225-68-2P, 5-[1-[(2-Fluorophenylcarbamoyl)methyl]-1H-pyrazol-3-yl]thiophene-2-carboxylic acid hydroxyamide 656225-70-6P, 5-[1-[(Quinolin-3-ylcarbamoyl)methyl]-1H-pyrazol-3-yl]thiophene-2-carboxylic acid hydroxyamide 656225-72-8P, 5-[1-[(Pyridin-3-ylcarbamoyl)methyl]-1H-pyrazol-3-yl]thiophene-2-carboxylic acid hydroxyamide 656225-74-0P, 5-[1-[2-(Quinolin-2-yl)ethyl]-1H-pyrazol-3-yl]thiophene-2-carboxylic acid hydroxyamide 656225-76-2P, 5-[1-[[(Pyridin-3-ylmethyl)carbamoyl]methyl]-1H-pyrazol-3-yl]thiophene-2-carboxylic acid hydroxyamide 656225-78-4P, 5-[1-[(Biphenyl-4-yl)methyl]-1H-pyrazol-3-yl]thiophene-2-carboxylic acid hydroxyamide 656225-80-8P, 5-[1-[[6-(2,2-Dimethylpropionylamino)pyridin-2-yl]methyl]-1H-pyrazol-3-yl]thiophene-2-carboxylic acid hydroxyamide 656225-82-0P, 5-[1-[2-(Biphenyl-4-yloxy)ethyl]-1H-pyrazol-3-yl]thiophene-2-carboxylic acid hydroxyamide 656225-84-2P, 5-[1-(3-Phenoxybenzyl)-1H-pyrazol-3-yl]thiophene-2-carboxylic acid hydroxyamide 656225-86-4P, 5-[1-[3-[4-(3-Chlorophenyl)piperazin-1-yl]propyl]-1H-pyrazol-3-yl]thiophene-2-carboxylic acid hydroxyamide 656225-88-6P, 5-[1-[[[4-(Morpholin-4-yl)phenyl]carbamoyl]methyl]-1H-pyrazol-3-yl]thiophene-2-carboxylic acid hydroxyamide 656225-90-0P, 5-[1-[[[2-(Morpholin-4-yl)phenyl]carbamoyl]methyl]-1H-pyrazol-3-yl]thiophene-2-carboxylic acid hydroxyamide 656225-92-2P, 5-[1-[[[4-(Oxazol-5-yl)phenyl]carbamoyl]methyl]-1H-pyrazol-3-yl]thiophene-2-carboxylic acid hydroxyamide 656225-94-4P, 5-[1-[(4-Acetylaminophenylcarbamoyl)methyl]-1H-pyrazol-3-yl]thiophene-2-carboxylic acid hydroxyamide 656225-96-6P, 5-[1-[(1-Oxoquinolin-2-yl)methyl]-1H-pyrazol-3-yl]thiophene-2-carboxylic acid hydroxyamide 656225-98-8P, 5-[1-[2-Oxo-2-[4-(4-trifluoromethylpyrimidin-2-yl)piperazin-1-yl]ethyl]-1H-pyrazol-3-yl]thiophene-2-carboxylic acid hydroxyamide 656226-00-5P, 5-[6-[[(Pyridin-3-ylmethyl)amino]methyl]pyridin-2-yl]thiophene-2-carboxylic acid hydroxyamide 656226-02-7P, 5-[6-[[[2-(Pyridin-3-yl)ethyl]amino]methyl]pyridin-2-yl]thiophene-2-carboxylic acid hydroxyamide 656226-04-9P, 5-[6-[(4-Fluorobenzylamino)methyl]pyridin-2-yl]thiophene-2-carboxylic acid hydroxyamide 656226-06-1P, 5-[6-[[[(Benzo[1,3]dioxol-5-yl)methyl]amino]methyl]pyridin-2-yl]thiophene-2-carboxylic acid hydroxyamide 656226-08-3P, 5-[6-[[(1H-Benzimidazol-2-ylmethyl)amino]methyl]pyridin-2-yl]thiophene-2-carboxylic acid hydroxyamide 656226-10-7P, 5-[6-[[[3-(Imidazol-1-yl)propyl]amino]methyl]pyridin-2-yl]thiophene-2-carboxylic acid hydroxyamide 656226-12-9P, 5-[6-[(4-Methoxyphenylamino)methyl]pyridin-2-yl]thiophene-2-carboxylic acid hydroxyamide 656226-14-1P, 5-[6-(Methylphenethylamino)pyridin-2-yl]thiophene-2-carboxylic acid hydroxyamide 656226-16-3P, 5-[6-[[Methyl(pyridin-3-ylmethyl)amino]methyl]pyridin-2-yl]thiophene-2-carboxylic acid hydroxyamide 656226-18-5P, 5-[6-[(1,2,3,4-Tetrahydro-1H-isoquinolin-2-yl)methyl]pyridin-2-yl]thiophene-2-carboxylic acid hydroxyamide 656226-20-9P, 5-[6-[[Methyl(naphthalen-1-ylmethyl)amino]methyl]pyridin-2-yl]thiophene-2-carboxylic acid hydroxyamide 656226-22-1P, 5-[6-[(4-Phenethylpiperazin-1-yl)methyl]pyridin-2-yl]thiophene-2-carboxylic acid hydroxyamide 656226-24-3P, 5-[6-[[4-(Pyridin-2-yl)piperazin-1-yl]methyl]pyridin-2-yl]thiophene-2-carboxylic acid hydroxyamide 656226-26-5P, 2-(5-Hydroxycarbamoylthiophen-2-yl)-5-methyl-

1H-imidazole-4-carboxylic acid phenethylamide 656226-28-7P, 2-(5-Hydroxycarbamoylthiophen-2-yl)-5-methyl-1H-imidazole-4-carboxylic acid benzylamide 656226-30-1P, 5-[6-[(Benzyloxy)methyl]pyridin-2-yl]thiophene-2-carboxylic acid hydroxyamide 656226-32-3P, 5-[6-(3-Phenylpropionylamino)pyridin-2-yl]thiophene-2-carboxylic acid hydroxyamide 656226-34-5P, 5-[1-[(3-Methoxyphenylcarbamoyl)methyl]-1H-pyrazol-3-yl]thiophene-2-carboxylic acid hydroxyamide 656226-36-7P, 5-[1-[(3-Chlorophenylcarbamoyl)methyl]-1H-pyrazol-3-yl]thiophene-2-carboxylic acid hydroxyamide 656226-38-9P, 5-[1-[(3,5-Difluorophenylcarbamoyl)methyl]-1H-pyrazol-3-yl]thiophene-2-carboxylic acid hydroxyamide 656226-40-3P, 5-[1-[(3-Sulfamoylphenylcarbamoyl)methyl]-1H-pyrazol-3-yl]thiophene-2-carboxylic acid hydroxyamide 656226-42-5P, 5-[1-[(1H-Indazol-7-ylcarbamoyl)methyl]-1H-pyrazol-3-yl]thiophene-2-carboxylic acid hydroxyamide 656226-44-7P, 5-[1-[(1H-Indol-7-ylcarbamoyl)methyl]-1H-pyrazol-3-yl]thiophene-2-carboxylic acid hydroxyamide 656226-46-9P, 5-[6-(3-Phenylpropylamino)pyridin-2-yl]thiophene-2-carboxylic acid hydroxyamide 656226-48-1P, 5-[1-[2-(Benzylamino)ethyl]-1H-pyrazol-3-yl]thiophene-2-carboxylic acid hydroxyamide 656226-50-5P, 5-[1-[3-[(Quinolin-2-ylmethyl)amino]propyl]-1H-pyrazol-3-yl]thiophene-2-carboxylic acid hydroxyamide 656226-52-7P, 5-[1-[3-[[(Benzo[1,3]dioxol-5-yl)methyl]amino]propyl]-1H-pyrazol-3-yl]thiophene-2-carboxylic acid hydroxyamide 656226-54-9P, 5-[1-[2-[[(Benzo[1,3]dioxol-5-yl)methyl]amino]ethyl]-1H-pyrazol-3-yl]thiophene-2-carboxylic acid hydroxyamide 656226-56-1P, 5-[1-[2-[(Pyridin-4-ylmethyl)amino]ethyl]-1H-pyrazol-3-yl]thiophene-2-carboxylic acid hydroxyamide 656226-58-3P, 5-[6-[[[(Benzo[1,3]dioxol-5-yl)methyl](methyl)amino]methyl]pyridin-2-yl]thiophene-2-carboxylic acid hydroxyamide 656227-59-7P, 5-[5-(2-Benzyloxyethylamino)pyridin-2-yl]thiophene-2-carboxylic acid hydroxyamide
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(drug candidate; preparation of thiophene-2-hydroxamic acids as **histone deacetylase** inhibitors useful against disorders involving increased cell proliferation)

IT **9076-57-7, Histone deacetylase**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(inhibitors; preparation of substituted thiophene-2-hydroxamic acids as **histone deacetylase** inhibitors useful against disorders involving increased cell proliferation)

IT 64-04-0, Phenethylamine 88-15-3, 2-Acetylthiophene 91-21-4, 1,2,3,4-Tetrahydroisoquinoline 98-18-0, 3-Aminobenzenesulfonamide 98-88-4, Benzoyl chloride 100-39-0, Benzyl bromide 100-44-7, Benzyl chloride, reactions 100-46-9, Benzylamine, reactions 100-52-7, Benzaldehyde, reactions 103-25-3, Methyl 3-phenylpropionate 103-63-9, (2-Bromoethyl)benzene 103-80-0, Phenylacetyl chloride 104-53-0, Hydrocinnamaldehyde 104-94-9, 4-Methoxyaniline 108-42-9, 3-Chloroaniline 120-57-0, Piperonal 122-78-1, Phenylacetaldehyde 140-75-0, 4-Fluorobenzylamine 332-42-3, 1-(2-Bromoethyl)-4-fluorobenzene 347-66-0, 2-Chloro-N-(2-fluorophenyl)acetamide 350-81-2, 2-Chloro-N-(3-fluorophenyl)acetamide 351-04-2, 2-Chloro-N-(4-fluorophenyl)acetamide 372-39-4, 3,5-Difluoroaniline 431-67-4, 1,1-Dibromo-3,3,3-trifluoroacetone 459-46-1, 4-Fluorobenzyl bromide 462-08-8, 3-Aminopyridine 536-90-3, 3-Aminoanisole 578-66-5, 8-Aminoquinoline 580-17-6, 3-Aminoquinoline 585-71-7, (1-Bromoethyl)benzene 587-65-5, 2-Chloro-N-phenylacetamide 588-63-6, 3-Phenoxypropyl bromide 589-08-2, N-Methylphenethylamine 626-05-1, 2,6-Dibromopyridine 626-55-1, 3-Bromopyridine 637-59-2, 1-Bromo-3-phenylpropane 645-45-4, Hydrocinnamoyl chloride 701-99-5, Phenoxyacetyl chloride 872-85-5, Isonicotinaldehyde 1462-37-9, Benzyl 2-bromoethyl ether 1667-11-4, 4-Phenylbenzyl chloride 1822-51-1, 4-Picolyl chloride hydrochloride 2060-55-1, [2,2']Bithiophenyl-5-carboxylic acid 2164-34-3, 2-Bromomethyl-1,4-benzodioxan 2361-27-5,

2-Thiophenecarboxylic hydrazide 2564-06-9, N-Benzyl-2-chloroacetamide 2606-51-1, 5-Bromomethylbenzo[1,3]dioxole 2620-50-0, [(Benzo[1,3]dioxol-5-yl)methyl]amine 2653-10-3, N-(4-Acetylaminophenyl)-2-chloroacetamide 3351-60-8, 4-(2-Bromoethoxy)-1,1'-biphenyl 3389-21-7, 3-(2-Bromoethyl)indole 3647-69-6, 4-(2-Chloroethyl)morpholine hydrochloride 3731-51-9, 2-(Aminomethyl)pyridine 3731-52-0, 3-Aminomethylpyridine 3747-74-8, 2-(Chloromethyl)quinoline hydrochloride 4066-41-5, 5-Acetylthiophene-2-carboxylic acid 4265-16-1, Benzo[b]furan-2-carboxaldehyde 4392-24-9, Cinnamyl bromide 4487-59-6, 2-Bromo-5-nitropyridine 4595-60-2, 2-Bromopyrimidine 4784-77-4, Crotyl bromide 5036-48-6, N-(3-Aminopropyl)imidazole 5192-04-1, 7-Aminoindole 5292-43-3, tert-Butyl bromoacetate 5321-49-3, 1-(2-Phenylethyl)piperazine 5470-96-2, 2-Quinolinecarboxaldehyde 5751-83-7, Ethyl 5-bromothiophene-2-carboxylate 5805-57-2, [(1H-Benzimidazol-2-yl)methyl]amine 5815-08-7, tert-Butoxybis(dimethylamino)methane 6723-30-4, O-(Tetrahydro-2H-pyran-2-yl)hydroxylamine 10601-80-6, Ethyl 3,3-diethoxypropionate 13156-95-1, 2-Chloro-N-phenethylacetamide 13679-72-6, 2-Acetyl-3-methylthiophene 14267-92-6, 5-Chloro-1-pentyne 14489-75-9, N-Methyl-1-naphthylmethylamine 19163-24-7, 5-Phenylthiophene-2-carboxylic acid 19524-06-2, 4-Bromopyridine hydrochloride 19798-81-3, 2-Amino-6-bromopyridine 20173-04-0, Methyl(pyridin-3-ylmethyl)amine 20173-24-4, 3-(2-Aminoethyl)pyridine 21443-96-9, 1H-Indazol-7-amine 26385-07-9, N-(2-Chloroethyl)benzamide 31108-35-7, 2,3-Dioxobutanoic acid tert-butyl ester 34160-40-2, 6-Bromopyridine-2-carboxaldehyde 34723-82-5, 2-(Bromomethyl)tetrahydro-2H-pyran 34803-66-2, 1-(2-Pyridyl)piperazine 39086-61-8, 2-Chloro-N-ethyl-N-phenylacetamide 39178-35-3, Isonicotinoyl chloride hydrochloride 39577-43-0, 1-(3-Chlorophenyl)-4-(3-chloropropyl)piperazine 39684-80-5, 2-[(tert-Butoxycarbonyl)amino]ethyl bromide 42458-71-9, 2-Chloro-N-[5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl]acetamide 52157-62-7, 2-(5-Bromothiophen-2-yl)-[1,3]dioxolane 52191-26-1, 3-[2-(2-Chloroacetamido)ethyl]indole 53874-66-1, 3-Phenoxybenzyl chloride 54610-75-2, 2-Thiophenecarboximidamide 55860-22-5, 2-Chloro-N-(2-methoxyphenyl)acetamide 64473-34-3, 1-Chloro-3-(4-chlorophenyl)propane 76253-74-2, 2-Chloromethylquinoline 1-oxide 83948-53-2, 3-[(tert-Butoxycarbonyl)amino]propyl bromide 87787-59-5, 1,4-Benzodioxin-6-carboxaldehyde 88653-55-8, 5-Acetylthiophene-2-carbonitrile 98440-32-5, Methanesulfonic acid 2-(4-trifluoromethylphenyl)ethyl ester 100779-91-7, 1-(3-Bromopropyl)pyrrole 111477-43-1, N-(6-Bromomethylpyridin-2-yl)-2,2-dimethylpropionamide 116016-56-9, 5-(4-Methoxyphenyl)thiophene-2-carboxylic acid 119082-97-2, 5-(Pyridin-2-yl)thiophene-2-carboxylic acid 133380-68-4, 5-(3-Methyl-[1,2,4]oxadiazol-5-yl)thiophene-2-carboxylic acid 170655-46-6, 2-Chloro-N-[4-(morpholino)phenyl]acetamide 175202-29-6, 5-[2-Methyl-5-(trifluoromethyl)-2H-pyrazol-3-yl]thiophene-2-carboxylic acid 175205-41-1, 5-tert-Butyl-3-(chloromethyl)-1,2,4-oxadiazole 202191-13-7, Quinoline-2-carboxylic acid (2-chloroethyl)amide 214360-76-6, 3-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)phenol 223499-10-3, 5-(5-Trifluoromethyl-1H-pyrazol-3-yl)thiophene-2-carboxylic acid 223499-20-5, 5-(1-Methyl-5-trifluoromethyl-1H-pyrazol-3-yl)thiophene-2-carboxylic acid 278791-54-1, 2-Chloro-1-[4-[4-(trifluoromethyl)pyrimidin-2-yl]piperazino]ethan-1-one 303151-23-7, 2-Chloro-N-[2-(morpholino)phenyl]acetamide 337508-56-2, 1-(Bromomethyl)isoquinoline hydrobromide 465515-31-5, 5-(Dihydroxyboryl)-2-thiophenecarboxylic acid 648409-03-4, N-[4-(1,3-Oxazol-5-yl)phenyl]-2-chloroacetamide 656227-26-8, Methanesulfonic acid 2-(4-trifluoromethoxyphenyl)ethyl ester 656227-27-9, 2-Chloro-N-(2-trifluoromethoxyphenyl)acetamide 656227-28-0, Methanesulfonic acid 2-(quinolin-2-yl)ethyl ester
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of thiophene-2-hydroxamic acids as **histone deacetylase** inhibitors useful against disorders involving increased cell proliferation)

IT 319-56-2P, 4,4,4-Trifluoro-1-[3-(methyl)thiophen-2-yl]butane-1,3-dione 67808-64-4P, 5-Formylthiophene-2-carboxylic acid methyl ester 125903-92-6P, 2-(Thiophen-2-yl)pyrimidin-4-ol 216867-32-2P, 5-(Pyridin-4-yl)thiophene-2-carboxylic acid 278803-20-6P, 5-(Pyridin-3-yl)thiophene-2-carboxylic acid 474707-58-9P, 5-(1H-Pyrazol-3-yl)thiophene-2-carbonitrile 474707-59-0P, 5-(1H-Pyrazol-3-yl)thiophene-2-carboxylic acid methyl ester 656224-28-1P, 5-(2-Methyl-5-trifluoromethyl-2H-pyrazol-3-yl)thiophene-2-carboxylic acid (tetrahydropyran-2-yloxy)amide 656224-30-5P, 5-(2-Methyl-2H-pyrazol-3-yl)thiophene-2-carboxylic acid (tetrahydropyran-2-yloxy)amide 656224-31-6P, 5-(1-Methyl-1H-pyrazol-3-yl)thiophene-2-carboxylic acid (tetrahydropyran-2-yloxy)amide 656224-34-9P, 5-(5-Trifluoromethyl-1H-pyrazol-3-yl)thiophene-2-carboxylic acid (tetrahydropyran-2-yloxy)amide 656224-36-1P, 5-(1-Methyl-5-trifluoromethyl-1H-pyrazol-3-yl)thiophene-2-carboxylic acid (tetrahydropyran-2-yloxy)amide 656224-38-3P, 5-(5-Trifluoromethylisoxazol-3-yl)thiophene-2-carboxylic acid (tetrahydropyran-2-yloxy)amide 656224-40-7P, 5-Phenylthiophene-2-carboxylic acid (tetrahydropyran-2-yloxy)amide 656224-42-9P, 5-(Pyridin-2-yl)thiophene-2-carboxylic acid (tetrahydropyran-2-yloxy)amide 656224-44-1P, [2,2']Bithiophenyl-5-carboxylic acid (tetrahydropyran-2-yloxy)amide 656224-46-3P, 5-(4-Methoxyphenyl)thiophene-2-carboxylic acid [(tetrahydropyran-2-yl)oxy]amide 656224-48-5P, 5-(2H-Pyrazol-3-yl)thiophene-2-carboxylic acid (tetrahydropyran-2-yloxy)amide 656224-50-9P, 5-(1-Benzyl-1H-pyrazol-3-yl)thiophene-2-carboxylic acid (tetrahydropyran-2-yloxy)amide 656224-52-1P, 5-(1-Phenethyl-1H-pyrazol-3-yl)thiophene-2-carboxylic acid (tetrahydropyran-2-yloxy)amide 656224-54-3P, 5-(4-Trifluoromethyl-1H-imidazol-2-yl)thiophene-2-carboxylic acid (tetrahydropyran-2-yloxy)amide 656224-56-5P, 5-(3-Methyl-[1,2,4]oxadiazol-5-yl)thiophene-2-carboxylic acid (tetrahydropyran-2-yloxy)amide 656224-58-7P, 5-[1-[2-(Benzyloxy)ethyl]-1H-pyrazol-3-yl]thiophene-2-carboxylic acid methyl ester 656224-60-1P, 5-[1-(3-Phenylpropyl)-1H-pyrazol-3-yl]thiophene-2-carboxylic acid (tetrahydropyran-2-yloxy)amide 656224-62-3P, 5-[1-[(2,3-Dihydrobenzo[1,4]dioxin-2-yl)methyl]-1H-pyrazol-3-yl]thiophene-2-carboxylic acid (tetrahydropyran-2-yloxy)amide 656224-64-5P, 5-[1-[2-(4-Trifluoromethylphenyl)ethyl]-1H-pyrazol-3-yl]thiophene-2-carboxylic acid (tetrahydropyran-2-yloxy)amide 656224-66-7P, 5-[1-[(Benzo[1,3]dioxol-5-yl)methyl]-1H-pyrazol-3-yl]thiophene-2-carboxylic acid (tetrahydropyran-2-yloxy)amide 656224-68-9P, 5-[1-[2-(4-Trifluoromethoxyphenyl)ethyl]-1H-pyrazol-3-yl]thiophene-2-carboxylic acid (tetrahydropyran-2-yloxy)amide 656224-70-3P, 5-[1-[2-(4-Fluorophenyl)ethyl]-1H-pyrazol-3-yl]thiophene-2-carboxylic acid (tetrahydropyran-2-yloxy)amide 656224-72-5P, 5-[1-(1-Phenylethyl)-1H-pyrazol-3-yl]thiophene-2-carboxylic acid (tetrahydropyran-2-yloxy)amide 656224-74-7P, 5-[1-[2-(Morpholin-4-yl)ethyl]-1H-pyrazol-3-yl]thiophene-2-carboxylic acid (tetrahydropyran-2-yloxy)amide 656224-76-9P, 5-[1-(Tetrahydropyran-2-ylmethyl)-1H-pyrazol-3-yl]thiophene-2-carboxylic acid (tetrahydropyran-2-yloxy)amide 656224-78-1P, 5-[4-(Benzyloxy)pyrimidin-2-yl]thiophene-2-carboxylic acid (tetrahydropyran-2-yloxy)amide 656224-80-5P, 5-(5-Phenethyl-1H-pyrazol-3-yl)thiophene-2-carboxylic acid (tetrahydropyran-2-yloxy)amide 656224-82-7P, 5-(2-Phenethyl-1H-imidazol-4-yl)thiophene-2-carboxylic acid (tetrahydropyran-2-yloxy)amide 656224-84-9P, 5-(Pyrimidin-2-yl)thiophene-2-carboxylic acid (tetrahydropyran-2-yloxy)amide 656224-86-1P, 5-(1-Phenethyl-5-trifluoromethyl-1H-pyrazol-3-yl)thiophene-2-carboxylic acid (tetrahydropyran-2-yloxy)amide 656224-88-3P, 5-(Pyridin-3-yl)thiophene-2-carboxylic acid (tetrahydropyran-2-yloxy)amide 656224-90-7P, 5-(Pyridin-4-yl)thiophene-2-carboxylic acid (tetrahydropyran-2-yloxy)amide 656224-92-9P, 5-(5-Trifluoromethyl-1H-[1,2,4]triazol-3-yl)thiophene-2-carboxylic acid (tetrahydropyran-2-yloxy)amide 656224-94-1P, 5-[5-(3-Phenylpropionylamino)pyridin-2-yl]thiophene-2-carboxylic acid methyl ester 656224-97-4P,

5-[3-(Benzyloxy)phenyl]thiophene-2-carboxylic acid (tetrahydropyran-2-yloxy)amide 656224-99-6P, 5-(5-Phenethylaminopyridin-2-yl)thiophene-2-carboxylic acid methyl ester 656225-02-4P, 5-(1-Pent-4-ynyl-1H-pyrazol-3-yl)thiophene-2-carboxylic acid methyl ester 656225-04-6P, 5-[1-(3-Phenylallyl)-1H-pyrazol-3-yl]thiophene-2-carboxylic acid methyl ester 656225-06-8P, 5-[1-(3-Phenoxypropyl)-1H-pyrazol-3-yl]thiophene-2-carboxylic acid methyl ester 656225-08-0P, 5-[1-[2-(Benzoylamino)ethyl]-1H-pyrazol-3-yl]thiophene-2-carboxylic acid methyl ester 656225-10-4P, 5-[1-[(Pyridin-4-yl)methyl]-1H-pyrazol-3-yl]thiophene-2-carboxylic acid methyl ester 656225-13-7P, 5-[1-[(5-tert-Butyl-[1,2,4]oxadiazol-3-yl)methyl]-1H-pyrazol-3-yl]thiophene-2-carboxylic acid methyl ester 656225-15-9P, 5-[1-[3-(Pyrrol-1-yl)propyl]-1H-pyrazol-3-yl]thiophene-2-carboxylic acid methyl ester 656225-17-1P, 5-(1-But-2-enyl-1H-pyrazol-3-yl)thiophene-2-carboxylic acid methyl ester 656225-19-3P, 5-[5-(2-Phenoxyacetylamino)pyridin-2-yl]thiophene-2-carboxylic acid methyl ester 656225-21-7P, 5-[5-[(Phenylacetyl)amino]pyridin-2-yl]thiophene-2-carboxylic acid methyl ester 656225-23-9P, 5-[1-[(Quinolin-2-yl)methyl]-1H-pyrazol-3-yl]thiophene-2-carboxylic acid methyl ester 656225-25-1P, 5-[5-(Benzoylamino)pyridin-2-yl]thiophene-2-carboxylic acid methyl ester 656225-27-3P, 5-[5-[[(Pyridin-4-yl)carbonyl]amino]pyridin-2-yl]thiophene-2-carboxylic acid methyl ester 656225-29-5P, 5-[5-[(Quinolin-2-ylmethyl)amino]pyridin-2-yl]thiophene-2-carboxylic acid methyl ester 656225-31-9P, 5-[5-[[(2,3-Dihydrobenzo[1,4]dioxin-6-yl)methyl]amino]pyridin-2-yl]thiophene-2-carboxylic acid methyl ester 656225-33-1P, 5-[5-[(Benzofuran-2-ylmethyl)amino]pyridin-2-yl]thiophene-2-carboxylic acid methyl ester 656225-35-3P, 5-[1-[2-(4-Fluorobenzyloxy)ethyl]-1H-pyrazol-3-yl]thiophene-2-carboxylic acid methyl ester 656225-37-5P, 5-[1-[(Phenylcarbamoyl)methyl]-1H-pyrazol-3-yl]thiophene-2-carboxylic acid methyl ester 656225-39-7P, 5-[1-[[(Pyridin-2-ylmethyl)carbamoyl]methyl]-1H-pyrazol-3-yl]thiophene-2-carboxylic acid methyl ester 656225-41-1P, 5-[1-[(Quinolin-8-ylcarbamoyl)methyl]-1H-pyrazol-3-yl]thiophene-2-carboxylic acid methyl ester 656225-43-3P, 5-[1-[[(5-Trifluoromethyl-[1,3,4]thiadiazol-2-yl)carbamoyl]methyl]-1H-pyrazol-3-yl]thiophene-2-carboxylic acid methyl ester 656225-45-5P, 5-[1-[(2-Methoxyphenylcarbamoyl)methyl]-1H-pyrazol-3-yl]thiophene-2-carboxylic acid methyl ester 656225-47-7P, 5-[1-[(4-Fluorophenylcarbamoyl)methyl]-1H-pyrazol-3-yl]thiophene-2-carboxylic acid methyl ester 656225-49-9P, 5-[1-[(3-Fluorophenylcarbamoyl)methyl]-1H-pyrazol-3-yl]thiophene-2-carboxylic acid methyl ester 656225-51-3P, 5-[1-[2-[[(Quinolin-2-yl)carbonyl]amino]ethyl]-1H-pyrazol-3-yl]thiophene-2-carboxylic acid methyl ester 656225-53-5P, 5-[1-[(Benzylcarbamoyl)methyl]-1H-pyrazol-3-yl]thiophene-2-carboxylic acid methyl ester 656225-55-7P, 5-[1-[(N-Ethyl-N-phenylcarbamoyl)methyl]-1H-pyrazol-3-yl]thiophene-2-carboxylic acid methyl ester 656225-57-9P, 5-[1-[2-(1H-Indol-3-yl)ethyl]-1H-pyrazol-3-yl]thiophene-2-carboxylic acid methyl ester 656225-59-1P, 5-[1-[(2-Trifluoromethoxyphenylcarbamoyl)methyl]-1H-pyrazol-3-yl]thiophene-2-carboxylic acid methyl ester 656225-61-5P, 5-[1-[3-(4-Chlorophenyl)propyl]-1H-pyrazol-3-yl]thiophene-2-carboxylic acid methyl ester 656225-63-7P, 5-[1-[[[2-(1H-Indol-3-yl)ethyl]carbamoyl]methyl]-1H-pyrazol-3-yl]thiophene-2-carboxylic acid methyl ester 656225-65-9P, 5-[1-[(Phenethylcarbamoyl)methyl]-1H-pyrazol-3-yl]thiophene-2-carboxylic acid methyl ester 656225-67-1P, 5-[1-[(Isoquinolin-1-yl)methyl]-1H-pyrazol-3-yl]thiophene-2-carboxylic acid methyl ester 656225-69-3P, 5-[1-[(2-Fluorophenylcarbamoyl)methyl]-1H-pyrazol-3-yl]thiophene-2-carboxylic acid methyl ester 656225-71-7P, 5-[1-[(Quinolin-3-ylcarbamoyl)methyl]-1H-pyrazol-3-yl]thiophene-2-carboxylic acid methyl ester 656225-73-9P, 5-[1-[(Pyridin-3-ylcarbamoyl)methyl]-1H-pyrazol-3-yl]thiophene-2-carboxylic acid methyl ester 656225-75-1P, 5-[1-[2-(Quinolin-2-yl)ethyl]-1H-pyrazol-3-yl]thiophene-2-carboxylic acid methyl ester 656225-77-3P, 5-[1-[[(Pyridin-3-ylmethyl)carbamoyl]methyl]-1H-pyrazol-3-yl]thiophene-2-carboxylic acid methyl ester 656225-79-5P, 5-(1-Biphenyl-4-ylmethyl-1H-pyrazol-3-yl)thiophene-2-carboxylic acid

methyl ester 656225-81-9P, 5-[1-[[6-(2,2-Dimethylpropionylamino)pyridin-2-yl]methyl]-1H-pyrazol-3-yl]thiophene-2-carboxylic acid methyl ester 656225-83-1P, 5-[1-[2-(Biphenyl-4-yloxy)ethyl]-1H-pyrazol-3-yl]thiophene-2-carboxylic acid methyl ester 656225-85-3P, 5-[1-(3-Phenoxybenzyl)-1H-pyrazol-3-yl]thiophene-2-carboxylic acid methyl ester 656225-87-5P, 5-[1-[3-[4-(3-Chlorophenyl)piperazin-1-yl]propyl]-1H-pyrazol-3-yl]thiophene-2-carboxylic acid methyl ester 656225-89-7P, 5-[1-[[[4-(Morpholin-4-yl)phenyl]carbamoyl]methyl]-1H-pyrazol-3-yl]thiophene-2-carboxylic acid methyl ester 656225-91-1P, 5-[1-[[[2-(Morpholin-4-yl)phenyl]carbamoyl]methyl]-1H-pyrazol-3-yl]thiophene-2-carboxylic acid methyl ester 656225-93-3P, 5-[1-[[[4-(Oxazol-5-yl)phenyl]carbamoyl]methyl]-1H-pyrazol-3-yl]thiophene-2-carboxylic acid methyl ester 656225-95-5P, 5-[1-[(4-Acetylaminophenylcarbamoyl)methyl]-1H-pyrazol-3-yl]thiophene-2-carboxylic acid methyl ester 656225-97-7P, 5-[1-[(1-Oxoquinolin-2-yl)methyl]-1H-pyrazol-3-yl]thiophene-2-carboxylic acid (tetrahydropyran-2-yloxy)amide 656225-99-9P, 5-[1-[2-Oxo-2-[4-(4-trifluoromethylpyrimidin-2-yl)piperazin-1-yl]ethyl]-1H-pyrazol-3-yl]thiophene-2-carboxylic acid methyl ester 656226-01-6P, 5-[6-[[(Pyridin-3-ylmethyl)amino]methyl]pyridin-2-yl]thiophene-2-carboxylic acid (tetrahydropyran-2-yloxy)amide 656226-03-8P, 5-[6-[[[2-(Pyridin-3-yl)ethyl]amino]methyl]pyridin-2-yl]thiophene-2-carboxylic acid (tetrahydropyran-2-yloxy)amide 656226-05-0P, 5-[6-[(4-Fluorobenzylamino)methyl]pyridin-2-yl]thiophene-2-carboxylic acid (tetrahydropyran-2-yloxy)amide 656226-07-2P, 5-[6-[[[(Benzo[1,3]dioxol-5-yl)methyl]amino]methyl]pyridin-2-yl]thiophene-2-carboxylic acid (tetrahydropyran-2-yloxy)amide 656226-09-4P, 5-[6-[[(1H-Benzimidazol-2-ylmethyl)amino]methyl]pyridin-2-yl]thiophene-2-carboxylic acid (tetrahydropyran-2-yloxy)amide 656226-11-8P, 5-[6-[[[3-(Imidazol-1-yl)propyl]amino]methyl]pyridin-2-yl]thiophene-2-carboxylic acid (tetrahydropyran-2-yloxy)amide 656226-13-0P, 5-[6-[(4-Methoxyphenylamino)methyl]pyridin-2-yl]thiophene-2-carboxylic acid 656226-15-2P, 5-[6-(Methylphenethylamino)pyridin-2-yl]thiophene-2-carboxylic acid 656226-17-4P, 5-[6-[[Methyl(pyridin-3-ylmethyl)amino]methyl]pyridin-2-yl]thiophene-2-carboxylic acid 656226-19-6P, 5-[6-[(1,2,3,4-Tetrahydro-1H-isoquinolin-2-yl)methyl]pyridin-2-yl]thiophene-2-carboxylic acid 656226-21-0P, 5-[6-[[Methyl(naphthalen-1-ylmethyl)amino]methyl]pyridin-2-yl]thiophene-2-carboxylic acid 656226-23-2P, 5-[6-[(4-Phenethylpiperazin-1-yl)methyl]pyridin-2-yl]thiophene-2-carboxylic acid 656226-25-4P, 5-[6-[[4-(Pyridin-2-yl)piperazin-1-yl]methyl]pyridin-2-yl]thiophene-2-carboxylic acid 656226-27-6P, 5-(5-Methyl-4-phenethylcarbamoyl-1H-imidazol-2-yl)thiophene-2-carboxylic acid methyl ester 656226-29-8P, 5-(4-Benzylcarbamoyl-5-methyl-1H-imidazol-2-yl)thiophene-2-carboxylic acid methyl ester 656226-31-2P, 5-[6-[(Benzyloxy)methyl]pyridin-2-yl]thiophene-2-carboxylic acid methyl ester 656226-33-4P, 5-[6-(3-Phenylpropionylamino)pyridin-2-yl]thiophene-2-carboxylic acid (tetrahydropyran-2-yloxy)amide 656226-35-6P, 5-[1-[(3-Methoxyphenylcarbamoyl)methyl]-1H-pyrazol-3-yl]thiophene-2-carboxylic acid (tetrahydropyran-2-yloxy)amide 656226-37-8P, 5-[1-[(3-Chlorophenylcarbamoyl)methyl]-1H-pyrazol-3-yl]thiophene-2-carboxylic acid methyl ester 656226-39-0P, 5-[1-[(3,5-Difluorophenylcarbamoyl)methyl]-1H-pyrazol-3-yl]thiophene-2-carboxylic acid methyl ester 656226-41-4P, 5-[1-[(3-Sulfamoylphenylcarbamoyl)methyl]-1H-pyrazol-3-yl]thiophene-2-carboxylic acid methyl ester 656226-43-6P, 5-[1-[(1H-Indazol-7-ylcarbamoyl)methyl]-1H-pyrazol-3-yl]thiophene-2-carboxylic acid methyl ester 656226-45-8P, 5-[1-[(1H-Indol-7-ylcarbamoyl)methyl]-1H-pyrazol-3-yl]thiophene-2-carboxylic acid methyl ester 656226-47-0P, 5-[6-(3-Phenylpropylamino)pyridin-2-yl]thiophene-2-carboxylic acid methyl ester 656226-49-2P, 5-[1-[2-(Benzylamino)ethyl]-1H-pyrazol-3-yl]thiophene-2-carboxylic acid 656226-51-6P, 5-[1-[3-[(Quinolin-2-ylmethyl)amino]propyl]-1H-pyrazol-3-yl]thiophene-2-carboxylic acid 656226-53-8P, 5-[1-[3-[[(Benzo[1,3]dioxol-5-yl)methyl]amino]propyl]-1H-pyrazol-3-yl]thiophene-2-carboxylic acid 656226-55-0P,

5-[1-[2-[[(Benzo[1,3]dioxol-5-yl)methyl]amino]ethyl]-1H-pyrazol-3-yl]thiophene-2-carboxylic acid 656226-57-2P, 5-[1-[2-[(Pyridin-4-ylmethyl)amino]ethyl]-1H-pyrazol-3-yl]thiophene-2-carboxylic acid 656226-59-4P, 5-[6-[[[(Benzo[1,3]dioxol-5-yl)methyl](methyl)amino]methyl]pyridin-2-yl]thiophene-2-carboxylic acid (tetrahydropyran-2-yloxy)amide 656226-60-7P, 5-(2-Methyl-2H-pyrazol-3-yl)thiophene-2-carboxylic acid 656226-61-8P, 5-(1-Methyl-1H-pyrazol-3-yl)thiophene-2-carboxylic acid 656226-62-9P, 5-(5-Hydroxy-5-trifluoromethyl-4,5-dihydroisoxazol-3-yl)thiophene-2-carboxylic acid 656226-63-0P, 5-(1H-Pyrazol-3-yl)thiophene-2-carboxylic acid 656226-64-1P, 5-(1-Benzyl-1H-pyrazol-3-yl)thiophene-2-carboxylic acid 656226-65-2P, 5-(1-Phenethyl-1H-pyrazol-3-yl)thiophene-2-carboxylic acid 656226-66-3P, 5-(4-Trifluoromethyl-1H-imidazol-2-yl)thiophene-2-carboxylic acid 656226-67-4P, 5-[1-(3-Phenylpropyl)-1H-pyrazol-3-yl]thiophene-2-carboxylic acid 656226-68-5P, 5-[1-[(2,3-Dihydrobenzo[1,4]dioxin-2-yl)methyl]-1H-pyrazol-3-yl]thiophene-2-carboxylic acid 656226-69-6P, 5-[1-[2-(4-Trifluoromethylphenyl)ethyl]-1H-pyrazol-3-yl]thiophene-2-carboxylic acid 656226-70-9P, 5-[1-[(Benzo[1,3]dioxol-5-yl)methyl]-1H-pyrazol-3-yl]thiophene-2-carboxylic acid 656226-71-0P, 5-[1-[2-(4-Trifluoromethoxyphenyl)ethyl]-1H-pyrazol-3-yl]thiophene-2-carboxylic acid 656226-72-1P, 5-[1-[2-(4-Fluorophenyl)ethyl]-1H-pyrazol-3-yl]thiophene-2-carboxylic acid 656226-73-2P, 5-[1-(1-Phenylethyl)-1H-pyrazol-3-yl]thiophene-2-carboxylic acid 656226-74-3P, 5-[1-[2-(Morpholin-4-yl)ethyl]-1H-pyrazol-3-yl]thiophene-2-carboxylic acid 656226-75-4P, 5-[1-(Tetrahydropyran-2-ylmethyl)-1H-pyrazol-3-yl]thiophene-2-carboxylic acid 656226-76-5P, 5-[4-(Benzyloxy)pyrimidin-2-yl]thiophene-2-carboxylic acid 656226-77-6P, 5-(5-Phenethyl-1H-pyrazol-3-yl)thiophene-2-carboxylic acid 656226-78-7P, 5-(2-Phenethyl-1H-imidazol-4-yl)thiophene-2-carboxylic acid 656226-79-8P, 5-(Pyrimidin-2-yl)thiophene-2-carboxylic acid 656226-80-1P, 5-(1-Phenethyl-5-trifluoromethyl-1H-pyrazol-3-yl)thiophene-2-carboxylic acid 656226-81-2P, 5-(5-Trifluoromethyl-1H-[1,2,4]triazol-3-yl)thiophene-2-carboxylic acid 656226-82-3P, 4-Methyl-5-(5-trifluoromethyl-1H-pyrazol-3-yl)thiophene-2-carboxylic acid 656226-83-4P, 5-[3-(Benzyloxy)phenyl]thiophene-2-carboxylic acid 656226-84-5P, 5-[6-[[(Pyridin-3-ylmethyl)amino]methyl]pyridin-2-yl]thiophene-2-carboxylic acid 656226-85-6P, 5-[6-[[[2-(Pyridin-3-yl)ethyl]amino]methyl]pyridin-2-yl]thiophene-2-carboxylic acid 656226-86-7P, 5-[6-[(4-Fluorobenzylamino)methyl]pyridin-2-yl]thiophene-2-carboxylic acid 656226-87-8P, 5-[6-[[[(Benzo[1,3]dioxol-5-yl)methyl]amino]methyl]pyridin-2-yl]thiophene-2-carboxylic acid 656226-88-9P, 5-[6-[[(1H-Benzimidazol-2-ylmethyl)amino]methyl]pyridin-2-yl]thiophene-2-carboxylic acid 656226-89-0P, 5-[6-[[[3-(Imidazol-1-yl)propyl]amino]methyl]pyridin-2-yl]thiophene-2-carboxylic acid 656226-90-3P, 5-[6-(3-Phenylpropionylamino)pyridin-2-yl]thiophene-2-carboxylic acid 656226-91-4P, 5-[1-[(3-Methoxyphenylcarbamoyl)methyl]-1H-pyrazol-3-yl]thiophene-2-carboxylic acid 656226-92-5P, 5-[6-(3-Phenylpropylamino)pyridin-2-yl]thiophene-2-carboxylic acid (tetrahydropyran-2-yloxy)amide 656226-93-6P, 5-[6-(3-Phenylpropylamino)pyridin-2-yl]thiophene-2-carboxylic acid 656226-94-7P, 5-[6-[[[(Benzo[1,3]dioxol-5-yl)methyl](methyl)amino]methyl]pyridin-2-yl]thiophene-2-carboxylic acid 656226-95-8P, 5-[1-[(1-Oxoquinolin-2-yl)methyl]-1H-pyrazol-3-yl]thiophene-2-carboxylic acid 656226-96-9P, 5-(2-Methyl-2H-pyrazol-3-yl)thiophene-2-carbonitrile 656226-97-0P , 5-(1-Methyl-1H-pyrazol-3-yl)thiophene-2-carbonitrile 656226-98-1P, 5-(5-Trifluoromethylisoxazol-3-yl)thiophene-2-carbonitrile 656226-99-2P, 5-(1-Benzyl-1H-pyrazol-3-yl)thiophene-2-carbonitrile 656227-00-8P, 5-(1-Phenethyl-1H-pyrazol-3-yl)thiophene-2-carbonitrile 656227-01-9P, 5-[1-(3-Phenylpropyl)-1H-pyrazol-3-yl]thiophene-2-carbonitrile 656227-02-0P, 5-[1-[(2,3-Dihydrobenzo[1,4]dioxin-2-yl)methyl]-1H-pyrazol-3-yl]thiophene-2-carbonitrile 656227-03-1P, 5-[1-[2-(4-Trifluoromethylphenyl)ethyl]-1H-pyrazol-3-yl]thiophene-2-carbonitrile 656227-04-2P, 5-[1-[(Benzo[1,3]dioxol-5-yl)methyl]-1H-pyrazol-3-yl]thiophene-2-carbonitrile 656227-05-3P, 5-[1-[2-(4-

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RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

(preparation of thiophene-2-hydroxamic acids as **histone deacetylase** inhibitors useful against disorders involving increased cell proliferation)

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TI MS-27-275, an inhibitor of **histone deacetylase**, has marked in vitro and in vivo antitumor activity against pediatric solid tumors
AU Jaboin, Jerry; Wild, Jason; Hamidi, Habib; Khanna, Chand; Kim, Chong Jai; Robey, Robert; Bates, Susan E.; Thiele, Carol J.
CS Cell and Molecular Biology Section, Pediatric Oncology Branch, Center for Cancer Research, National Cancer Institute, Bethesda, MD, 20892, USA
SO Cancer Research (2002), 62(21), 6108-6115
CODEN: CNREA8; ISSN: 0008-5472
PB American Association for Cancer Research
DT Journal
LA English
CC 1-6 (Pharmacology)
AB The antitumor efficacy of the synthetic benzamide derivative MS-27-275 (MS-275), an inhibitor of histone deacetylation, was evaluated in a series of pediatric solid tumor cell lines, including neuroblastoma, rhabdomyosarcoma, Ewing's sarcoma (EWS), retinoblastoma, medulloblastoma, undifferentiated sarcoma (US), osteosarcoma, and malignant rhabdoid tumors. Treatment with MS-275 results in an increase in acetylation of histones within 4 h of drug exposure. The cell lines were treated with various concns. of MS-275 for 3 days and incubated with [3H]thymidine for 20 h before cell harvest. MS-275 inhibited [3H]thymidine uptake in a dose-dependent manner in all tumor cell lines examined The IC50 ranged from 50 nm in the D283 medulloblastoma cell line to 1.3 μM in the US. A common feature of MS-275 treatment of pediatric tumor cell lines was induction of p21 mRNA. However, the effects on cell cycle were diverse because in some cases MS-275 induced an increase in G1 or G2, whereas in others, there was an induction of apoptosis. In EWS, the EWS/fli chimeric transcription factor created by the t(11;22) suppresses transforming growth factor (TGF) βRII transcription, however, MS-275 was able to induce an increase in TGF-βRII mRNA and restore TGF-β signaling. Using xenograft orthotopic models of US, EWS, and neuroblastoma, we find that the growth of established tumors is inhibited in mice treated with MS-275.
ST antitumor MS275 **histone deacetylase** cell cycle apoptosis
IT Bone, neoplasm
(Ewing's sarcoma; **histone deacetylase** inhibitor MS-27-275 has antitumor activity against pediatric solid tumors)
IT Histones
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(H3, acetylation; **histone deacetylase** inhibitor MS-27-275 has antitumor activity against pediatric solid tumors)
IT Transcription factors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(N-myc; **histone deacetylase** inhibitor MS-27-275 has antitumor activity against pediatric solid tumors)
IT Transforming growth factor receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(TGF-β receptor, type II; **histone deacetylase** inhibitor MS-27-275 has antitumor activity against pediatric solid tumors)
IT Transcription factors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(c-myc; **histone deacetylase** inhibitor MS-27-275 has

antitumor activity against pediatric solid tumors)
IT Development, mammalian postnatal
(child; **histone deacetylase** inhibitor MS-27-275 has antitumor activity against pediatric solid tumors)
IT Antitumor agents
Apoptosis
Cell cycle
Human
(**histone deacetylase** inhibitor MS-27-275 has antitumor activity against pediatric solid tumors)
IT Brain, neoplasm
(medulloblastoma; **histone deacetylase** inhibitor MS-27-275 has antitumor activity against pediatric solid tumors)
IT Nerve, neoplasm
(neuroblastoma; **histone deacetylase** inhibitor MS-27-275 has antitumor activity against pediatric solid tumors)
IT Bone, neoplasm
(osteosarcoma; **histone deacetylase** inhibitor MS-27-275 has antitumor activity against pediatric solid tumors)
IT Cyclin dependent kinase inhibitors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(p21CIP1; **histone deacetylase** inhibitor MS-27-275 has antitumor activity against pediatric solid tumors)
IT **Eye, neoplasm**
(**retinoblastoma; histone deacetylase** inhibitor MS-27-275 has antitumor activity against pediatric solid tumors)
IT Brain, neoplasm
(rhabdoid; **histone deacetylase** inhibitor MS-27-275 has antitumor activity against pediatric solid tumors)
IT Myoma
(rhabdomyosarcoma; **histone deacetylase** inhibitor MS-27-275 has antitumor activity against pediatric solid tumors)
IT Neoplasm
(solid; **histone deacetylase** inhibitor MS-27-275 has antitumor activity against pediatric solid tumors)
IT Sarcoma
(undifferentiated; **histone deacetylase** inhibitor MS-27-275 has antitumor activity against pediatric solid tumors)
IT **9076-57-7, Histone deacetylase**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(**histone deacetylase** inhibitor MS-27-275 has antitumor activity against pediatric solid tumors)
IT 209783-80-2, MS 27-275
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**histone deacetylase** inhibitor MS-27-275 has antitumor activity against pediatric solid tumors)
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